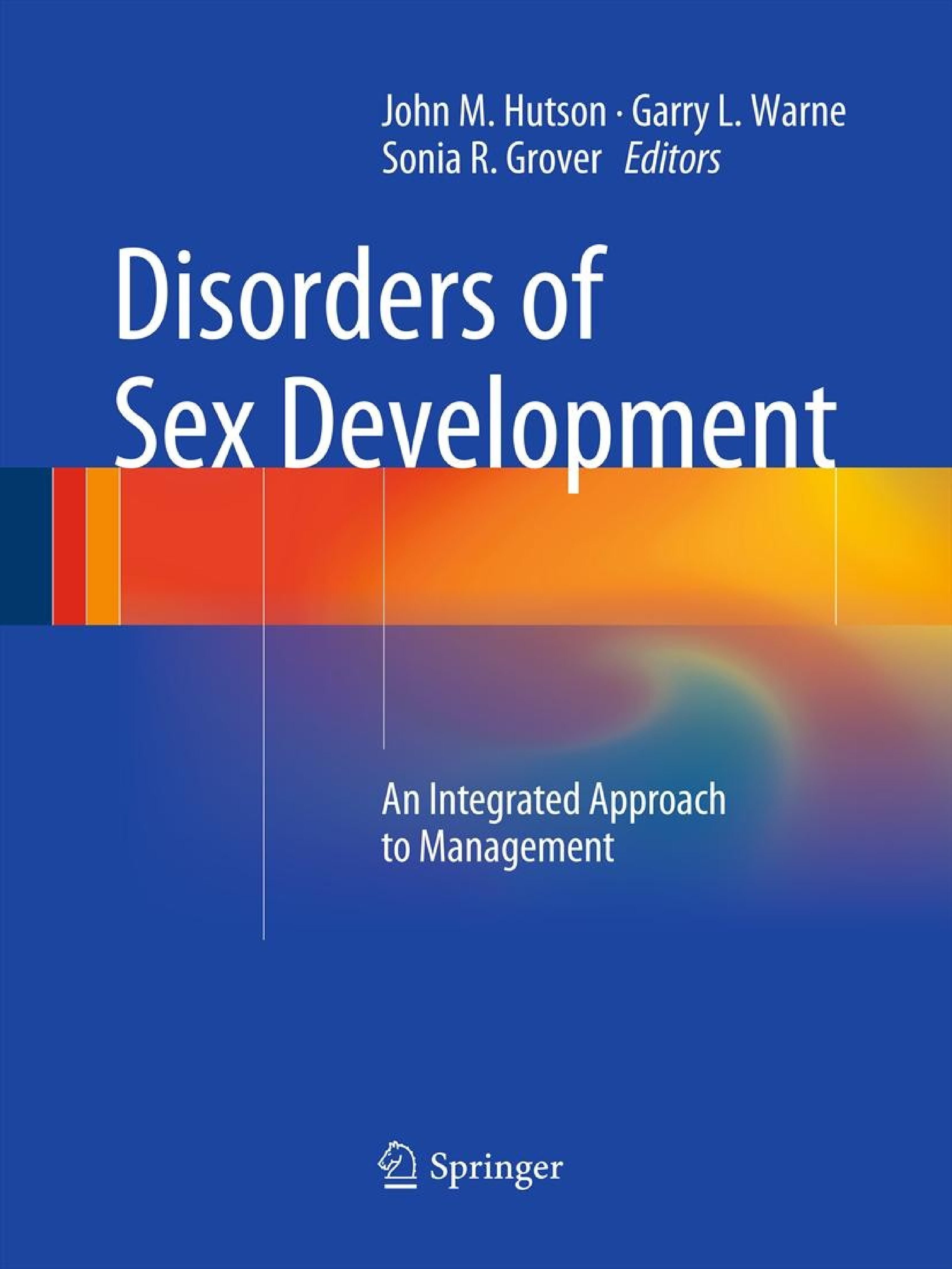

John M. Hutson · Garry L. Warne
Sonia R. Grover *Editors*

Disorders of Sex Development

An Integrated Approach to Management

Springer

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Editors

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Preface

> Art is long, and Time is fleeting,
> And our hearts, though stout and brave,
> Still, like muffled drums, are beating
> Funeral marches to the grave
>
> The Reaper and the Flowers
> Henry Wadsworth Longfellow

Two of us, John M. Hutson and Garry L. Warne, have spent our entire careers looking after patients with disorders of sex development (DSD). And as in all human interactions, we have learnt as much as we have taught. DSD present a specific combination of difficulties for clinicians grappling with their management: they are both extremely complex as well as rare, making acquisition of expertise a unique challenge. It was obvious in the 1970s that concentration of clinical experience with these conditions into a small group of committed doctors was a way to gain and then retain the special knowledge needed to provide these people with the best care – optimal medical and surgical treatment, appropriate counselling as well as moral support and empathy. Nearly everything we have learnt has come from our patients and for that we are extremely grateful. This volume is an attempt to preserve all of this knowledge for the next generation of patients and clinicians coming to terms with DSD.

The book contains many special features which we hope the readers, clinicians, parents and patients alike will be able to benefit from. We have tried to make the embryology of sex development understandable, and many of the chapters contain numerous diagrams that aim to make what to many people is an invisible mystery not only visible but also comprehensible. This emphasis extends to the chapters describing how to work out the diagnosis, as this is much easier when one understands the embryology. This culminates in Chap. 11, where we describe the 'rules for clinical diagnosis', which have been invaluable to us, as can be used by others also.

Another feature of the book is the clinical photographs of the anatomical details. Unlike the previous generation of endocrinology textbooks, there are no full frontal nude photographs of patients, being treated like 'specimens'. We learnt from our patients how much they hated being treated like a 'freak', and full body photography crosses this line. Instead, the photographs, that doctors need to learn about the disorders, are all close-up images of the genitalia and or perineum, with no identifying features about the individual patient. We hope our patients will understand that this special part of their anatomy needs to be seen by doctors, so that they can learn.

Gender assignment and the possible need for surgery in infants is a very controversial issue, and we have a chapter on all the ethical issues. Importantly, it describes the ethical principles we use to assess the proposed medical plan at birth, which have been endorsed by an international group of Family Law experts. It also includes our current algorithm for ethical assessment of medical plans in the neonatal period, so that there is a robust framework for these life-changing decisions.

Many DSD do not present until late in life, and the book contains a special section to describe these, so that clinicians can (hopefully) use these chapters to help resolve the underlying problems.

Babies with genital anomalies soon become children adolescents and adults, and we have put a lot of effort into providing chapters on all the issues that arise. In our chapter on DSD in childhood, we have a section on how to talk to pre-adolescent girls with Complete Androgen Insensitivity Syndrome (CAIS). This should be extremely useful to doctors struggling with the problem of how to broach the issues of XY chromosomes in a girl.

Finally, there are chapters on the long-term outcomes and the cultural differences of how DSD are seen in different societies. We end the book with a chapter written specifically for parents of a child with CAIS. This first appeared in the 1990s as a small booklet, but has been so much in demand we have reproduced it here, to ensure it remains available to parents hungry for information in the future.

Parkville, Australia John M. Hutson

Acknowledgements

First, we have to thank a generation of patients who were born with a DSD, for helping us learn how to do the job of managing them better. One of us, John M Hutson is extremely grateful to Mr. Robert Fowler, for first teaching him genital reconstruction in the 1970s, Prof. Patricia Donahoe, of Boston, Massachusetts, for not only being an inspirational academic surgeon, but also allowing him to study sexual development in the chick embryo, and to Mr. Justin Kelly for mentoring him for 5 years till he learnt the skills well enough to take over the surgical management of DSD for the next 25 years.

We also learnt a great deal from parent and patient support groups for Congenital Adrenal Hyperplasia (CAH), Androgen Insensitivity Syndrome (AIS) and Turner Syndrome as well as psychotherapeutic groups for women with vaginal agenesis. These were pioneered at our hospital by Garry L. Warne and allied health professionals, especially our Endocrine Social Worker, Elizabeth Loughlin. Paediatricians need to hear the experiences and priorities of adults affected by DSD and gain the opportunity of meeting them face to face by participating in and supporting support-group functions.

As the younger member of this team, I (Sonia Grover) would like to acknowledge the teaching and patience of John and Garry as well as the understanding of my patients, whilst I gathered the language and skills to talk about all of the personal and sensitive issues associated with DSD.

Finally, we thank Ms. Shirley D’Cruz for patiently, and extremely competently, turning this dream into a reality, with all her secretarial skill.

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1

The Molecular Basis of Gonadal Development and Disorders of Sex Development

Stefan White and Andrew Sinclair

Disorders of sex development (DSD) are congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical (Hughes et al. 2006). DSD represent a major paediatric concern due to the difficulty of clinical management of these complex conditions and their common sequelae of gonadal cancer and infertility. The cause of these problems is most often a breakdown of the complex network of gene regulation responsible for proper development of testes or ovaries in the embryo. Mutation studies in humans and mice have identified a number of genes that play critical roles in testis and ovary development. In this chapter we review some of the key genes involved in gonad development and show how defects in these genes result in DSD (Table 1.1).

1.1 Testis Development

1.1.1 SRY

In humans both males and females have 22 pairs of autosomal chromosomes, but differ in their sex chromosome complement. Females have two X chromosomes (46,XX) whereas males have one X and one Y chromosome (46,XY). This distinction was presumed to be the cause of the difference between males and females, and individuals with unusual sex chromosome numbers (e.g. 45,X females and 47,XXY males) suggested that a gene on the Y chromosome was responsible for male development. Attempts to identify the exact sequence responsible (referred to as the testis determining factor [TDF]) eventually focused on males with a 46,XX karyotype that had translocations containing small pieces of the Y chromosome. Molecular studies localised the gene translocated from the Y to the X chromosome, as the long-sought-after testis-determining gene, named *SRY* (*s*ex-determining *r*egion on the *Y* chromosome; Sinclair et al. 1990). There was further evidence supporting SRY as the critical testis determinant when point mutations within *SRY* were identified in several 46,XY females (Berta et al. 1990). Final proof that SRY was critical for male development was demonstrated when transgenic mouse studies showed that the addition of *Sry* alone was sufficient for XX mice to develop as males (Koopman et al. 1991). Many studies since these have shown that translocations of the *SRY* gene account for approximately 90% of 46,XX testicular DSD, whereas point mutations in *SRY* account for only about 15% of 46,XY gonadal dysgenesis cases (Cameron and Sinclair 1997).

1.1.1.1 SRY Gene and Protein

In mammals the *SRY* gene consists of a single exon, although the protein product can vary in size. *SRY* is a member of the high mobility group (HMG) domain-containing gene family. Outside of the HMG domain, *SRY* shows limited sequence conservation between species, suggesting that it is this domain that is crucial in initiating the male pathway. This is supported by the observation

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Table 1.1 Genes associated with disorders of sex development

Gene	Loss of function/haploinsufficiency	Gain of function/duplication
SRY	46,XY gonadal dysgenesis	46,XX testicular DSD
SOX9	46,XY gonadal dysgenesis with campomelic dysplasia	46,XX testicular DSD
NR5A1 (SF1)	46,XY gonadal dysgenesis with adrenal failure	
NR0B1 (DAX1)	Adrenal hypoplasia congenital and hypogonadotrophic hypogonadism	46,XY gonadal dysgenesis
WNT4		46,XY gonadal dysgenesis
RSPO1	46,XX testicular DSD with hyperkeratosis	
WT1	WAGR syndrome, Denys-Drash syndrome, Frasier syndrome	
CBX2	46,XY DSD	
FOXL2	BPES with ovarian failure	
DMRT1	46,XY gonadal dysgenesis	

that the vast majority of *SRY* mutations in DSD patients are found within the HMG domain (Cameron and Sinclair 1997). In the mouse, however, it has been shown that a C-terminal CAG repeat domain (not found in human SRY) is required for male sex determination (Bowles et al. 1999). The SRY HMG domain contains signal sequences that can direct SRY to the nucleus, where it is assumed to play a role in transcriptional regulation (Poulat et al. 1995). This domain also allows SRY to bind to DNA in a sequence-specific manner and alter chromatin conformation (Giese et al. 1992). In humans SRY is expressed from embryonic day (E) 41, peaks shortly thereafter and then remains present at low levels beyond embryogenesis (Hanley et al. 2000). In contrast, Sry expression in the mouse is limited to a transient period in the genital ridge of male mice from E10.5 to E12.5.

1.1.2 SOX9

SOX9 is a member of the SRY-related HMG box protein family. A role for SOX9 in testis development was first suggested in 1994 when mutations in and around *SOX9* were identified in patients with 46,XY gonadal dysgenesis and campomelic dysplasia (a syndrome characterised by a range of severe skeletal malformations; Foster et al. 1994; Wagner et al. 1994). A duplication including *SOX9* has also been described in a 46,XX DSD individual (Huang et al. 1999).

Animal studies have shown that knocking out *Sox9* in the developing gonad of XY mice embryos leads to ovarian development (Barrionuevo et al. 2006), whereas overexpressing *Sox9* in XX mice resulted in testis formation (Vidal et al. 2001).

Sox9 is expressed at a low level in the genital ridge at E10.5 in the mouse (Morais da Silva et al. 1996). As this expression in XY embryos increases shortly after Sry induction, it is thought that *Sox9* is (directly or indirectly) a target of Sry. This is supported by the finding that it is only precursor cells of the bipotential gonad expressing Sry that show an increase in Sox9 expression and subsequently develop into Sertoli cells (Sekido et al. 2004).

Identifying DNA sequences that control gonad-specific *SOX9* expression has proven problematic. The range of genomic DNA over which deletions and translocations around *SOX9* have been described (reviewed in Gordon et al. 2009) suggests that multiple regulatory elements are involved.

Sekido and Lovell-Badge defined a 3.2 kb testis-specific enhancer of Sox9 (TES) in the mouse (Sekido and Lovell-Badge 2008). Further analysis refined this region further to 1.4 kb, which they referred to as TESCO (TES core element). Functional analysis using reporter constructs containing TESCO showed that Sry and Sf1 were required to initiate Sox9 upregulation. The working model proposed that once Sox9 expression was initiated in the bipotential gonad, it was able to maintain its own high level of expression via a positive feedback loop (Sekido and Lovell-Badge 2009).

1.1.3 Steroidogenic Factor 1 (SF1)

SF1, also known as NR5A1 or AD4BP, is a nuclear receptor family member that is involved in both gonadal and adrenal development (Val and Swain 2009). It is expressed in the urogenital ridge, along with the developing hypothalamus and pituitary. Mutations in *SF1* cause 46,XY gonadal dysgenesis and adrenal failure (Achermann et al. 1999), whereas mutations in 46,XX individuals are associated with a range of conditions, including 46,XX gonadal dysgenesis and primary ovarian insufficiency (Lourenco et al. 2009).

SF1 is expressed in the bipotential gonad prior to the onset of SRY. Reporter construct studies suggest that SF1 can upregulate SRY expression (de Santa Barbara et al. 2001), although SF1 also has gonad-specific functions post-differentiation. In concert with SOX9, SF1 controls the level of MIS/AMH expression (Arango et al. 1999), and there is also evidence that other genes associated with gonad development are at least partially regulated by SF1 (Burris et al. 1995).

1.1.4 Wilms' Tumour-1 (WT1)

WT1 is a zinc finger-containing transcription factor that is primarily expressed during embryogenesis in mesodermally derived tissues, including the urogenital ridge, gonads and mesonephros (Armstrong et al. 1993). A mouse model containing a mutated *Wt1* failed to develop gonads and kidneys, resulting in embryonic lethality (Kreidberg et al. 1993). Mutations in *WT1* were first identified in children with Wilms' tumour. This tumour is also seen as part of WAGR syndrome, with other clinical characteristics including aniridia, genitourinary anomalies and mental retardation.

The gonadal abnormalities are recapitulated in other disorders where mutations in *WT1* have been described. Patients with Denys-Drash syndrome have a range of symptoms including gonadal abnormalities and renal failure (Pelletier et al. 1991). Frasier syndrome is characterised by 46,XY gonadal dysgenesis together with glomerulopathy (Barbaux et al. 1997). These patients have mutations that result in loss of a specific isoform of WT1 known as the +KTS type. This isoform has an additional three amino acids (K – lysine; T – threonine; S – serine) that are located between the third and fourth zinc finger.

These different isoforms play distinct roles during development. The –KTS isoform is able to bind to the *SRY* promoter region, leading to transactivation of the gene (Hossain and Saunders 2001). It can also bind to sequences within the promoter of *Sf1* (Wilhelm and Englert 2002). The +KTS isoform appears to be involved in regulating the amount of Sry transcript, as specifically knocking out this isoform in the mouse leads to reduced Sry levels (Hammes et al. 2001). This may be due to an effect on Sry mRNA stability, as the +KTS iso-form has been shown to have an affinity for RNA. There is also evidence that this isoform may function together with SF1 in increasing MIS/AMH expression (Arango et al. 1999), which is essential for inhibiting the development of the female-associated Müllerian structures.

1.1.5 Dosage-Sensitive Sex Reversal, Adrenal Hypoplasia Critical Region, X Chromosome Gene (DAX 1)

Some cases of 46,XY gonadal dysgenesis are associated with interstitial duplications within the short arm of the X chromosome (Baumstark et al. 1996; Sanlaville et al. 2004; Barbaro et al. 2007). This region, termed the dosage-sensitive sex-reversing (DSS) region, is thought to contain one or more genes that, when duplicated, block testis development. The best candidate is *DAX1* (also known as *NR0B1* [nuclear receptor subfamily 0, group B, member 1]), which falls within a 160-kb critical region defined by overlapping rearrangements in multiple cases.

The *DAX1* gene encodes an orphan receptor that does not have a zinc finger motif characteristic of other family members. It has been shown to bind to retinoic acid response elements, acting as a regulator of gene expression (Zanaria et al. 1994). There are conflicting data as to whether DAX1 protein has either a pro-testis or anti-testis role, as there is evidence for both functions. A duplication of *DAX1* in humans leads to 46,XY DSD, supporting an anti-testis function. In addition, loss-of-function mutations lead to hypogonadotrophic hypogonadism and adrenal hypoplasia congenita, with no effect on testis development (Muscatelli et al. 1994).

In the mouse Dax1 is normally expressed during hypothalamic, adrenal and gonadal development (Swain et al. 1996). Dax1 is expressed in both the developing testis and ovary, being down-regulated in the testis whilst expression is maintained in the ovary (Swain et al. 1998). Knocking out *Dax1* had no effect on ovarian development, whereas defects in testis development were observed (Yu et al. 1998). Over-expressing Dax1 also leads to gonadal abnormalities in XY mice, with the severity depending on the strain of mouse and level of SRY expression (Swain et al. 1998).

1.1.6 Dm-Related Transcription Factor 1 (DMRT1)

In humans *DMRT1* is located at the tip of chromosome 9p, and patients with a deletion including this region show a range of clinical features, including gonad abnormalities (Raymond et al. 1999; Calvari et al. 2000; Barbaro et al. 2009). *DMRT1* is the best candidate for the gonadal phenotype, but to date there have been no mutations identified within *DMRT1*. It has been suggested that the role of *DMRT1* in mammals may be at least partially compensated by related family members, especially *DMRT3*. Knocking out *Dmrt1* in the XY mouse, however, is still conducive to testis development, although there is disruption of post-natal testis differentiation (Raymond et al. 2000).

In a number of vertebrates *Dmrt1* is up-regulated in the developing genital ridge of male embryos (Moniot et al. 2000; Smith et al. 1999), with continued expression confined to the gonad. The role of *DMRT1* in sex determination has therefore been the subject of intense study in a range of model organisms.

In the chicken *Dmrt1* is located on the Z chromosome. Male chickens are the homogametic sex (ZZ), whereas female chickens are heterogametic (ZW). This suggests that the sex (testis)-determining gene in chickens could be present on the Z chromosome, acting in a dosage-dependent manner. Knock-down experiments *in ovo* showed that targeting *Dmrt1* mRNA with a shRNA in ZZ chicken embryos leads to feminisation of the gonads, strongly supporting the hypothesis that *Dmrt1* is a testis-determining gene in the chicken (Smith et al. 2009). Work in the medaka fish showed that a closely related gene (*dmy*), which is located on the Y chromosome, is the major testis-determining gene (Matsuda et al. 2002).

1.1.7 Fibroblast Growth Factor 9 (FGF9)

FGF9 is one of a number of growth factors involved in a broad range of developmental processes such as cell proliferation, survival, migration, and differentiation during embryonic development. *Fgf9* expression in the bipotential gonad is initiated immediately following *Sry*, and knocking out *Fgf9* in the mouse leads to male-to-female sex reversal associated with impaired development of the Sertoli cells (Colvin et al. 2001). In the absence of Fgf9, *Sox9* expression is not maintained, Sertoli cells fail to differentiate, testis development is aborted and the resulting somatic cells express genes characteristic of an ovary and the female developmental pathway. Data suggest that Sry initiates a positive feedback loop by up-regulating *Sox9* expression. This in turn up-regulates *Fgf9*, which then further up-regulates *Sox9* and propels the gonad down the testis pathway (Kim et al. 2006).

It now appears that Fgf9 mediates signalling through an FGF receptor (Fgfr2) that is found on the plasma membrane of these progenitor Sertoli cells. Fgfr2 is critical for Sertoli cell proliferation and differentiation in the developing testis. As a consequence, mutations in the human *FGFR2* gene may be responsible for some unexplained cases of DSD, although none have been reported yet (Kim et al. 2007).

1.1.8 Chromobox Homolog 2 (CBX2)

CBX2 is the human homolog of the mouse gene *M33*. Knocking out *M33* in mice affected the development of the genital ridge in both XX and XY embryos, suggesting that it functions upstream of *Sry*. The majority of XY mice showed sex reversal, whereas ovarian development was impaired in XX animals (Katoh-Fukui et al. 1998).

To date there has been only one report describing *CBX2* mutations in humans (Biason-Lauber et al. 2009). Two heterozygous missense mutations were identified in a 46,XY individual with a normal uterus and ovarian development, although these were not normal. Further analysis showed that each mutation was inherited from a different parent. A previous publication had shown that *Cbx2* was able to activate *Sf1* expression during spleen and adrenal development (Katoh-Fukui et al. 2005), and functional studies using luciferase reporter constructs demonstrated that this activation was impaired in the presence of either mutation. As these mutations were identified in a phenotypically normal female it was suggested that *CBX2* mutations may underlie some cases of infertility in women.

1.2 Ovarian Development

While many genes have been identified as part of the mammalian testis developmental pathway, until recently little was known about the underlying molecular mechanisms involved in ovarian development.

1.2.1 Wingless-Type MMTV Integration Site Family, Member 4 (Wnt4)

The *Wnt* gene family encodes proteins that are locally acting signalling molecules that play key roles in an array of developmental processes. One of the key *Wnt* genes in gonad development is *Wnt4*. The lack of *Wnt4* in XX mouse embryos resulted in masculinisation. These mice lacked Müllerian ducts and retained Wolffian structures, their oocytes degenerated and testosterone was produced (Vainio et al. 1999). Remarkably, a human patient was identified with a mutation in *WNT4* that had a similar phenotype to the *Wnt4* null mouse (Biason-Lauber et al. 2004).

Over-expression of Wnt4 in XY transgenic mice resulted in disruption of the normal testicular vasculature and inhibition of testosterone synthesis but these mice were not sex reversed (Jordan et al. 2003). This suggests that *Wnt4* is not the sole female sex-determining gene and that other genes are required to disrupt the male pathway and promote female (ovarian) development (Kim and Capel 2006). However, human patients with a duplication of chromosome 1p, including *WNT4*, showed a range of gonad anomalies including complete sex reversal (Jordan et al. 2001).

Wnt4 is up-regulated in developing female mouse gonads and appears to play a role in Müllerian duct formation, oocyte development and the sex-specific pattern of the vasculature. Furthermore, Wnts are known to exert their action through cytoplasmic β-catenin via the canonical Wnt-signalling pathway. Wnts can bind to a co-receptor LRP6 on the cell surface. This in turn results in non-phosphorylated (stabilised) β-catenin, which enters the nucleus and interacts with Tcf/Lef to up-regulate target gene transcription. In the absence of Wnt, β-catenin is phosphorylated, ultimately degraded and target genes are repressed (Bernard and Harley 2007). It is likely that *Wnt4* uses this canonical Wnt-signalling pathway in the developing gonad.

1.2.1.1 Antagonism Between WNT4 and FGF9

As previously mentioned, Fgf9 is expressed in Sertoli cell precursor cells and is critical for *Sox9* up-regulation. However, addition of Fgf9 to XX gonads in culture blocks *Wnt4* expression. These two findings suggest that FGF9 acts non-cell-autonomously to block female signals and recruit the early gonadal cell population into the male testis pathway. In a reciprocal way, *Wnt4* suppresses the male pathway. In *Wnt4*, mutant XX gonads Fgf9 and Sox9 are up-regulated, despite the absence of Sry (Kim and Capel 2006; Kim et al. 2006). Consequently, the presence of SRY is not critical for SOX9 up-regulation, as down-regulating WNT4 in an XX individual allows SOX9 to be up-regulated. This may well explain testicular tissue in XX male patients that are negative for SRY (Kim and Capel 2006). It has been suggested that antagonism between WNT4 and FGF9 balances the gonad between two alternate fates (Fig. 1.1). In XY individuals SRY

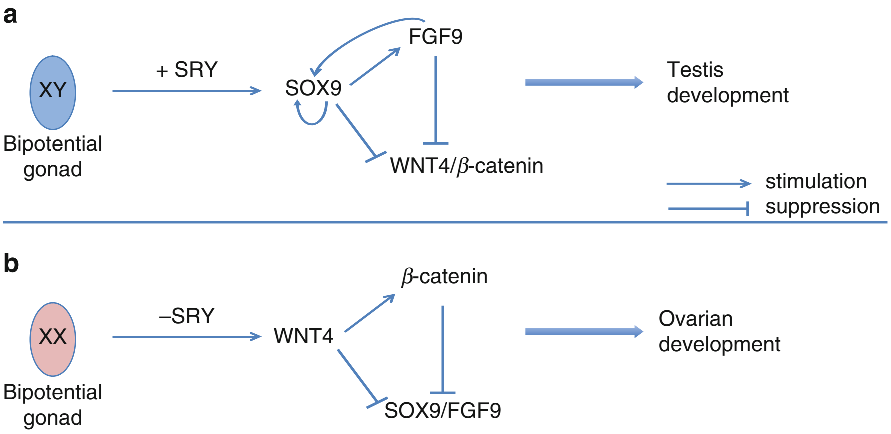

Fig. 1.1 Antagonistic pathways involved in gonad differentiation. (**a**) In XY individuals *SRY* is transiently expressed in the bipotential gonad. This initiates an increase in *SOX9* expression, which in turn stimulates FGF9. Both FGF9 and *SOX9* act together in a positive feedback loop, which suppresses WNT4 and leads to the establishment of the testis-specific pathway. (**b**) In the absence of *SRY* in XX individuals, WNT4 and β-catenin suppress the SOX9/FGF9 positive feedback loop, allowing the ovarian-specific pathway to progress

initiates a positive feedback loop between SOX9 and FGF9, which up-regulates FGF9 and represses WNT4, leading to establishment of the male (testis) pathway. In XX individuals, no SRY is present and WNT4 represses the positive feedback loop between SOX9 and FGF9, allowing the female (ovarian) pathway to become established. In this instance, the role of SRY, as a switch, is to tip the balance between these underlying patterns in favour of the testis pathway (Kim et al. 2006; Kim and Capel 2006).

1.2.2 R-Spondin1

R-Spondin1 (RSPO1) is part of a family of secreted growth factors that can stabilise β-catenin as part of the canonical Wnt-signalling pathway. It was implicated in ovarian development when a homozygous single nucleotide insertion within the *RSPO1* coding sequence was identified in four 46,XX testicular DSD individuals from a consanguineous family (Parma et al. 2006). The same report also described a homozygous exonic deletion in an unrelated sporadic case, and a separate study detected a homozygous splice-site mutation in a 46,XX ovotesticular DSD patient (Tomaselli et al. 2008). The variation in observed clinical features may be explained by the different consequences of the mutations, with the latter mutation leading to a partially functional protein.

This report was the first description showing that inactivation of a single gene is capable of causing female-to-male sex reversal, and the conserved expression pattern in other vertebrates suggests that it is a critical ovarian determinant.

Knocking out *Rspo1* in the mouse leads to masculinisation of XX gonads without complete sex reversal (Tomizuka et al. 2008). The canonical β-catenin pathway could not be activated in the absence of Rspo1, and there was no increase in *Wnt4* expression (Chassot et al. 2008).

1.2.3 Stabilisation of β-Catenin

In 46,XY males the *SRY* gene is thought to shift the bipotential gonad towards a testicular fate by initiating a positive feedback loop between SOX9 and FGF9. FGF9 has an antagonistic affect on the female pathway by repressing WNT4. In 46,XX female individuals both WNT4 and RSPO1 are known to promote ovarian development and repress testis development. In 46,XY female patients with duplication of chromosome 1p including both *WNT4* and *RSPO1*, testis development is suppressed allowing the ovarian pathway to dominate. Both WNT4 and RSPO1 activate the canonical Wnt signalling pathway. Recently it was shown that activation of stabilised β-catenin in an XY mouse disrupted testis development and caused male-to-female sex reversal (Maatouk et al. 2008). This suggests that β-catenin is a key ovarian and anti-testis signalling molecule. It follows that 46,XY female sex-reversed patients who have no apparent mutations in known testis-determining genes may arise through stabilisation of β-catenin, which negates the effects of SRY by destabilizing its critical downstream target, SOX9 (Maatouk et al. 2008).

1.2.4 Forkhead Transcription Factor Foxl2 (FOXL2)

FOXL2 is one of a number of winged helix/forkhead transcription factors (Hannenhalli and Kaestner 2009). A role for FOXL2 in ovarian development was first suggested with the identification of a deletion near *FOXL2* in the polled/intersex syndrome (PIS) goat (Pailhoux et al. 2001). Mutations in *FOXL2* in humans are associated with blepharo-phimosis/ptosis/epicanthus inversus syndrome (BPES), a condition characterised by eyelid defects with or without ovarian dysfunction (Crisponi et al. 2001). Knocking out *Foxl2* in the XX mouse leads to masculinisation of the supporting cells within the gonad (Ottolenghi et al. 2005), whereas knocking out both *Foxl2* and *Wnt4* in XX mice results in testis differentiation and the development of male germ cells (Ottolenghi et al. 2007).

In a remarkable recent study, it was shown that conditionally knocking out *Foxl2* in the adult mouse ovary caused transdifferentiation into testis (Uhlenhaut et al. 2009). The ovarian structure becomes more like that of a testis, with tubular features and Sertoli-like cells. Gene expression and in situ hybridisation studies showed up-regulation of a number of testis-specific genes, including Sox9. This finding suggests that Foxl2 plays a continuing role in maintaining the ovary, presumably by suppressing the pro-testis action of Sox9. Experimental evidence showed that this is most likely carried out together with Esr1/Esr2 by binding to sequences within the TESCO regulatory element controlling Sox9 expression. A clinically relevant aspect of this study is that somatic mutations in *FOXL2* may underlie some cases of ovarian dysfunction in adult females.

1.3 Conclusion

Since the discovery of *SRY* in 1990 a number of genes have been shown to be involved in gonad differentiation. Both testis and ovarian development involve pathways of distinct factors that act antagonistically. The normal role of SRY is to tip the balance in favour of the testis-specific pathway, and mutations in any of the key gonad genes can disrupt this balance sufficiently to cause aberrant gonad developmental and associated DSD.

It is likely that there are further genes remaining to be discovered in the gonad development pathway, and it is also probable that many unexplained DSD cases are due to disturbances of DNA sequences that control the expression of already known genes. Very little is understood about the regulation of genes described in this chapter; however this will be an area of intense scrutiny in the future.

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Embryology of the Human Genital Tract

2

John M. Hutson

2.1 The Urogenital Ridge

The genital tract is derived initially from the intermediate mesoderm of the urogenital ridge. The urogenital ridge contains the developing kidney, which includes at first the pronephros, then the mesonephros and finally the metanephros (Hutson 2008). In addition, the developing gonad forms anterior to the mesonephros and its duct, the mesonephric (Wolffian) duct. The mesonephros develops at approximately 4 weeks of gestation after the pronephros begins to degenerate. It also undergoes regression at approximately 7–8 weeks, which is at the time that the gonad begins to develop into ovary or testis. The mesonephric duct persists from the pronephric duct, and was originally named by Wolff. The paramesonephric or Müllerian duct develops as an evagination of the peritoneum adjacent to the gonad and migrates to the cloaca following the Wolffian duct (Fig. 2.1a–c).

The germ cells develop in the extra-embryonic tissues surrounding the yolk sac. Between 3 and 5 weeks of development they migrate around the yolk sac, through the caudal umbilical stalk and into the urogenital ridge (Fig. 2.1d, e). Once they arrive in the developing gonad they stimulate the development of the ovary or testis. In the developing ovary, the granulosa cells surround the germ cells and trigger meiotic arrest. By contrast, in the testis the newly formed Sertoli cells, which are derived from the surface epithelium of the gonad, enclose the primordial germ cells to form the testicular cords and trigger mitotic arrest of the germ cells (Fig. 2.2a–c).

2.1.1 Wolffian and Müllerian Duct Development

At the caudal end of the Wolffian duct, the metanephric mesenchyme of the urogenital ridge stimulates development of a ureteric bud from the Wolffian duct just before it reaches the cloaca. A ureteric bud will stimulate development of the definitive kidney or metanephros. When the cloaca separates into hindgut posteriorly and urogenital sinus anteriorly the distal end of the Wolffian duct beyond the ureteric bud becomes incorporated into the posterior surface of the urogenital sinus to form the trigone of the bladder. The caudal ends of the mesonephric ducts and ureters enlarge as they are incorporated into the urogenital sinus, and differential growth occurs so that ureters end up being cranial to the distal end of the Wolffian duct (Fig. 2.3).

The Müllerian ducts rotate antero-medially around the Wolffian ducts as they grow to the cloaca and fuse with each other. The distal end of the ducts contains no lumen and forms a solid utero-vaginal primordium, which contacts the endodermal urogenital sinus at the Müllerian tubercle. Proliferation of the endoderm of the tubercle produces the vaginal plate, which invades the utero-vaginal primordium to form the vaginal lumen by canalisation and also elongates caudally to bring the opening of the vagina to the exterior of the urogenital sinus (Figs. 2.4 and 2.5).

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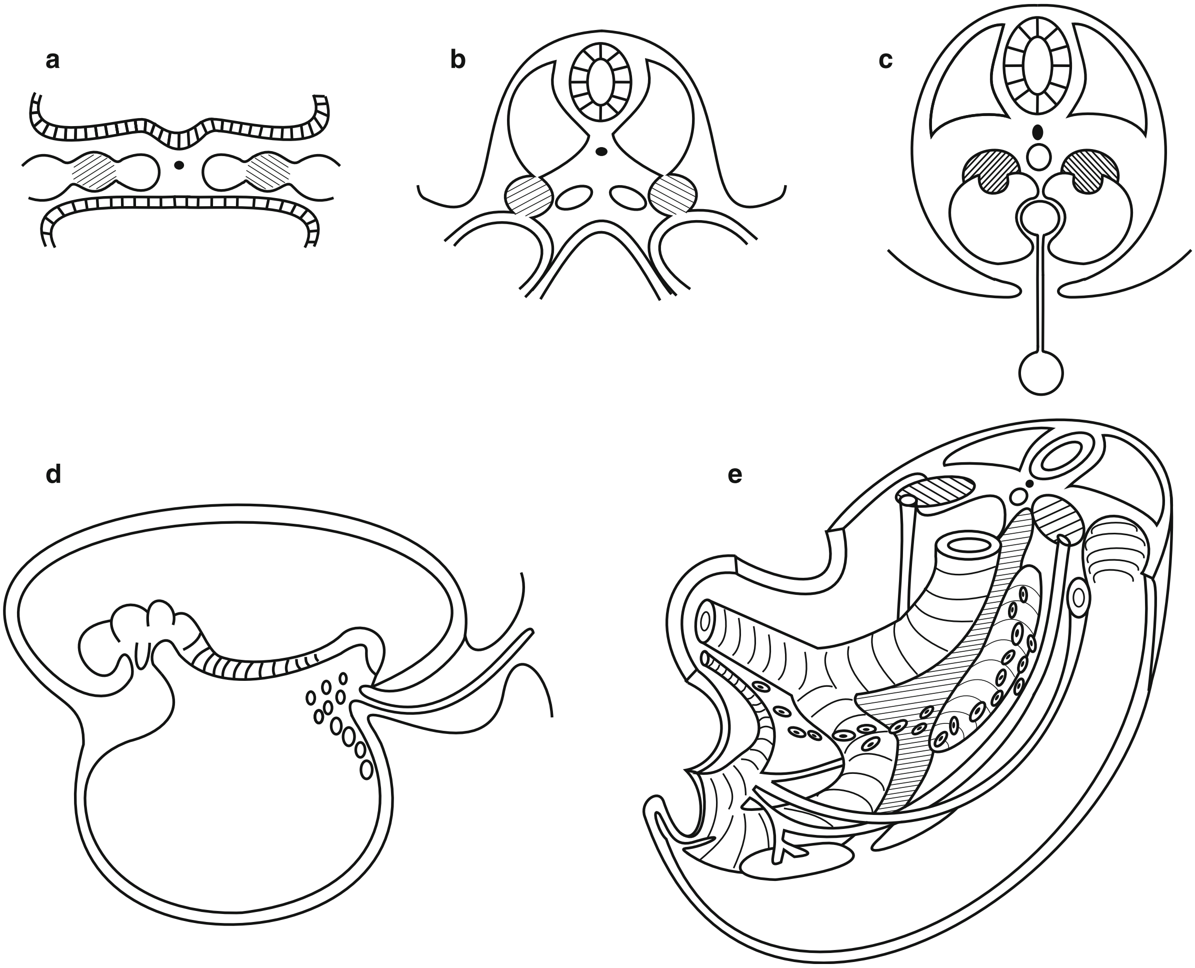


Fig. 2.1 Origin of the intermediate mesoderm in the early embryo. (**a**) Day 19. Transverse section of the trilaminar embryo showing the notochord and developing neural groove in the midline. The mesoderm forms into the paraxial mesoderm (the future somites), the intermediate mesoderm (the future urogenital tracts) and the lateral plate. (**b**).Day 21. The neural tube and dorsal aortas have formed, and the lateral plate mesoderm has split into parietal (somatic) and visceral layers. (**c**) Day 21–22. The embryo has now grown into a three-dimensional form. One dorsal aorta remains and the intermediate mesoderm is now proliferating and bulging into the future intraembryonic cavity (future pleura and peritoneum). (**d**) At 3 weeks, the primordial germ cells proliferate in the caudal wall of the yolk sac near the allantois. (**e**) Migration of the germ cells by amoeboid movement around the hindgut and through its dorsal mesentery to reach the retroperitoneum, and then into the urogenital ridges to reach the primitive gonads, which is required for their further normal development. Migration is regulated by Steel, fibronectin and laminin, and the primordial germ cells are visible because of expression of c-Kit, Oct4 and alkaline phosphatase

Abnormalities of Müllerian duct development include fusion defects, such as a bicornuate uterus or uterus didelphys. Failed canalisation of the primordium leads to uterine or vaginal atresia. One relatively common anomaly is obstruction of one hemivagina associated with absence of the ipsilateral kidney. This is caused by failure of the Wolffian duct to reach the cloaca, which prevents caudal migration of the ipsilateral Müllerian duct and prevents development of a ureteric bud (Rokitansky sequence) (Fig. 2.6) (Stephens et al. 2002).

2.2 Sexual Differentiation

At 7–8 weeks of development, regression of the mesonephros leaves the gonad suspended on a mesentery known as the mesogenitale. With sexual differentiation the gonad forms primary epithelial sex cords and mesenchymal medulla. Presence of XY chromosomes triggers activation of the SRY gene, which initiates development of a testis (as described in Chap. 1), where the primary sex cords develop into Sertoli cells (Fig. 2.2). The Sertoli cells produce Müllerian-inhibiting

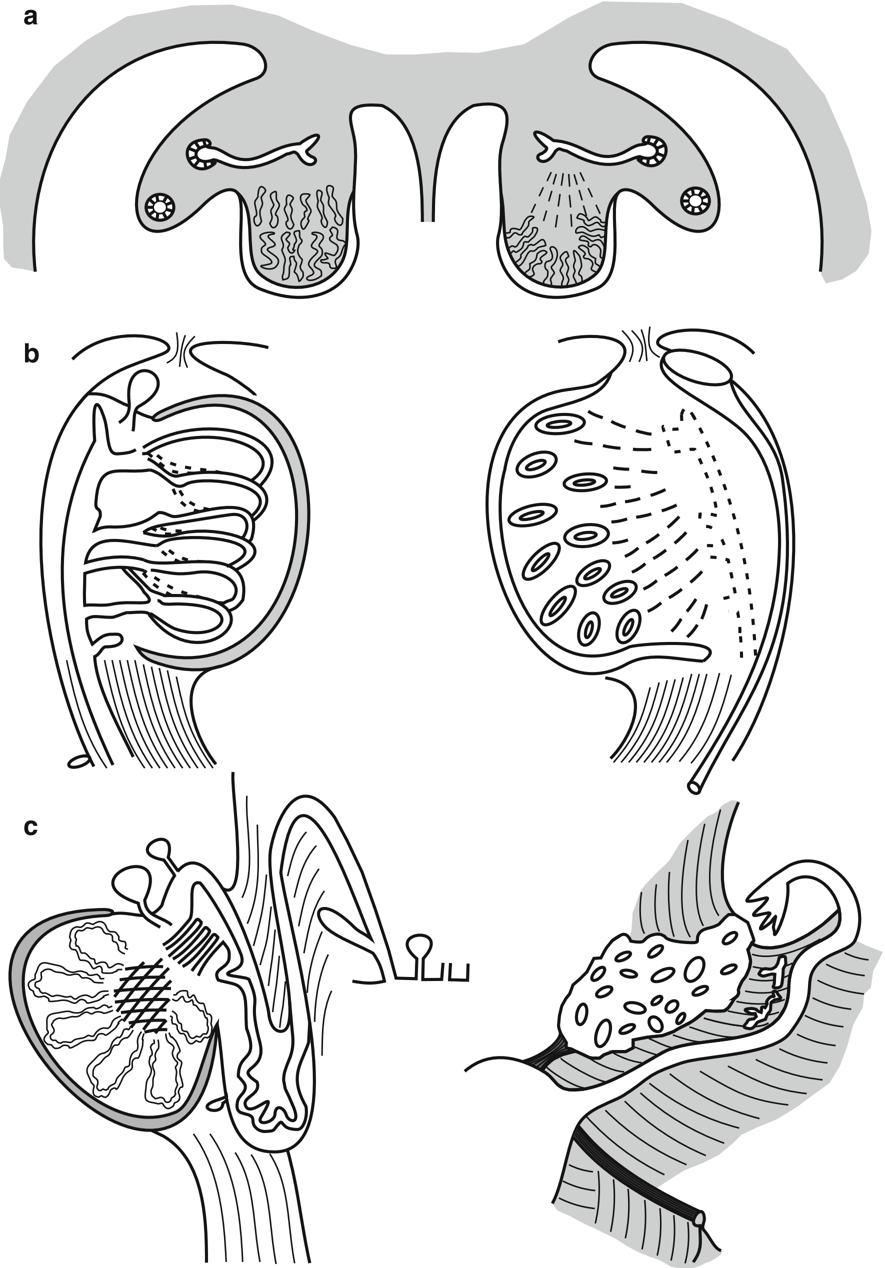


Fig. 2.2 (**a**) Transverse sections through the testis (on right side of embryo) and ovary (*left*) at 7–8 weeks. The testis is developing a tunica albuginea, a rete testis (from regressing mesonephric tubules) and primitive cords containing primordial germ cells. In the ovary the primitive medullary cords degenerate and the germ cells are in cortical cords, with proliferating surface epithelium. (**b**) The testis (on right side of embryo) has developed seminiferous cords (horseshoe-shaped) connected via the rete testis to the ductuli efferentes and the mesonephric (Wolffian) duct. The ovary has degenerated medullary cords and mesonephric tubules. The cortex has now developed primitive follicles around each germ cell. (**c**) The definitive genital ducts after testicular descent and formation of the broad ligament. The seminiferous tubules are in a horseshoe shape, connecting to the rete testis, efferent ductules and the developing epididymis. Caudally the vas deferens has a lateral diverticulum to form the seminal vesicle. Note cranial and caudal remnants of the paramesonephric (Müllerian) ducts: appendix testis (Hydatid of Morgagni) and prostatic utricle, respectively

substance, also known as anti-Müllerian hormone (MIS/AMH), which leads to regression of the Müllerian duct (Seifer and MacLaughlin 2007). Leydig cells form outside the testicular tubules and produce testosterone, which stimulates the Wolffian duct to persist to form the epididymis, vas deferens and seminal vesicles (Tong et al. 1996). Insulin-like hormone 3 (INSL3) is also produced from the Leydig cells and is important for development of the gubernaculum (Nef and Parada 1999; Zimmermann et al. 1999).

2.2.1 Testosterone

Testosterone was first synthesised in the 1940s, and is a steroid formed from cholesterol and progesterone in the Leydig cells. It is secreted into the bloodstream as well as down the Wolffian duct in an exocrine manner, exposing the Wolffian duct to very high concentrations (Tong et al. 1996) (Fig. 2.7a). In addition, testosterone is secreted in an endocrine manner into the bloodstream where it will act on the

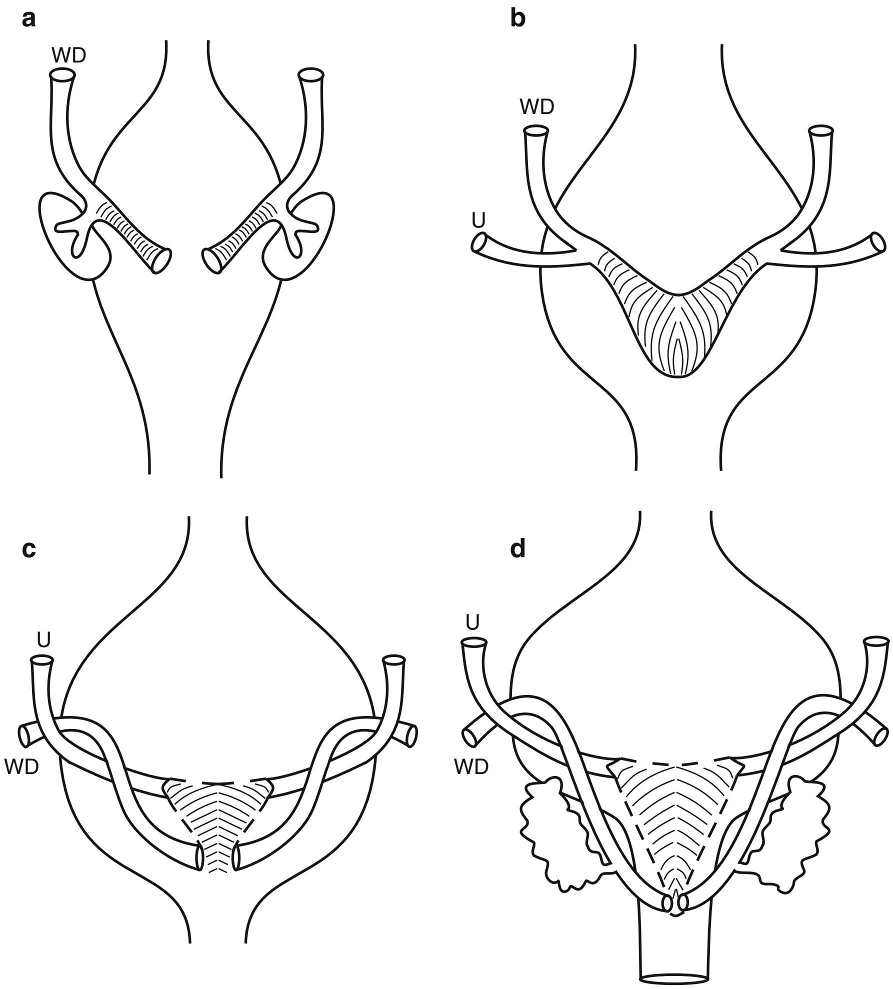


Fig. 2.3 The urogenital sinus, shown from behind, to demonstrate how the mesonephric duct below the ureteric bud is absorbed into the back wall of the urogenital sinus, to form the trigone of the bladder between the ureters, which migrate cranially around the lateral sides of the mesonephric ducts. (**a**) Common mesonephric ducts entering the urogenital sinus. (**b**) Common stem of mesonephric ducts being absorbed into back wall. (**c**) Origin of ureter rotating laterally around mesonephric duct to acquire independent opening into developing bladder. (**d**) Definitive anatomical arrangement with ureters opening into bladder at lateral corners of the trigone. Ejaculatory ducts enter into the prostatic urethra at the verumontanum. Seminal vesicles develop as lateral diverticula of caudal vasa deferentia

external genitalia to cause masculinisation. Sexual differentiation begins at approximately 8 weeks of gestation with production of MIS/AMH to trigger Müllerian duct regression, along with testosterone stimulating the Wolffian duct to persist to form the epididymis, vas deferens and seminal vesicles. The initial blood level of testosterone is probably too low to stimulate the external genital development without conversion to dihydrotestosterone (DHT) by the enzyme 5-alpha reductase type-2. Dihydrotestosterone binds about 5–10 times more tightly than testosterone itself to androgen receptors in the external genitalia, thereby increasing the effective concentration of testosterone ten-fold (Handelsman 2006). Some effects of testosterone in the brain may be mediated by conversion of testosterone to oestrogen via the enzyme aromatase, which is another mechanism to increase the effective concentration of androgen (Fig. 2.7b).

2.2.2 Müllerian-Inhibiting Substance/Anti-Müllerian Hormone (MIS/AMH)

Müllerian-inhibiting substance (MIS/AMH) was first synthesised in the 1980s, and is a glycoprotein dimer (~MW 140,000) produced by Sertoli cells. It is also secreted into the Wolffian duct and then diffuses laterally into the adjacent Müllerian duct to trigger its regression in the male. It may also have some secondary role in development of the gubernaculum, and has post-natal functions in the ovarian cycle (Seifer and MacLaughlin 2007).

2.2.3 Insulin-Like Hormone (INSL3)

Insulin-like hormone 3 (INSL3) was discovered in the 1990s, and is a protein with homology to insulin that is produced by Leydig cells. It stimulates growth of the

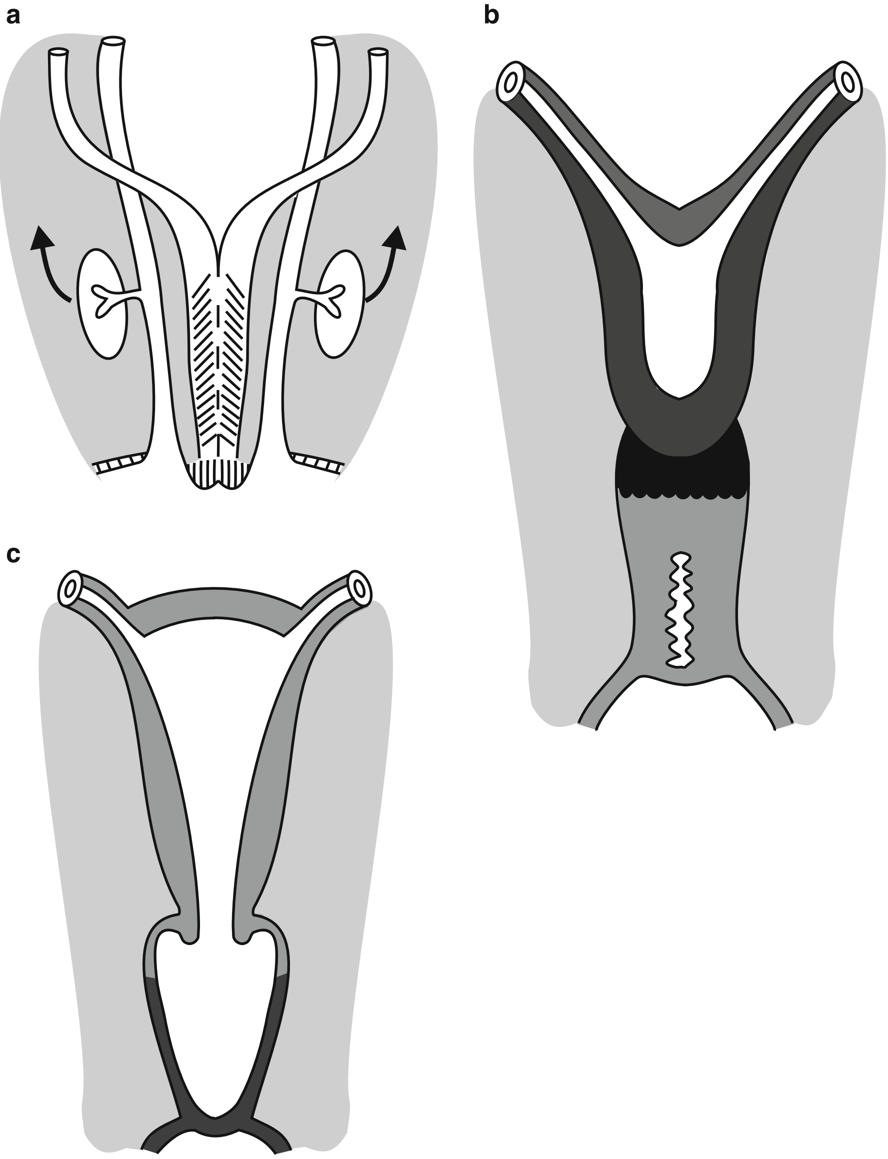


Fig. 2.4 Development of uterus and vagina. (**a**) Paramesonephric (Müllerian) ducts migrate to urogenital sinus, fusing with contralateral duct. Distal ends are solid. Contact of solid tips of paramesonephric ducts triggers proliferation of endoderm to form sino-vaginal bulb (Müllerian tubercle). (**b**) Proliferation of the bulb cells forms the vaginal plate, which begins to breakdown centrally to form a lumen. Meanwhile, a lumen is developing in the fused Müllerian ducts to form a single uterine cavity. (**c**) Late gestation with lumen in uterus and cervix and vaginal vault now in continuity with lumen within vaginal plate to form the vagina. The hymen breaks down to become patent before term

genito-inguinal ligament, or gubernaculum, which is important for the first phase of testicular descent (Zimmermann et al. 1999).

2.3 External Genitalia

The external genitalia remain undifferentiated until 8 weeks of development (Fig. 2.8a). Initially they contain a central genital tubercle surrounded by inner and outer genital folds. Between the inner genital folds lies the endodermal urethral plate and the urogenital sinus opening. Masculine development is triggered by DHT, causing growth of the genital tubercle into a penis, as well as growth of the perineal body to cover the urogenital sinus, canalisation of the urethral plate to form the urethra, and fusion of the outer genital folds to form the scrotum (Fig. 2.8b–d). In the female, the genital tubercle only enlarges a small amount to form the clitoris. In addition, there is apoptosis of the ventrally placed endoderm of the urethral plate, with leads to bending of the clitoral shaft. The inner genital folds remain separate to produce the labia minora, while the outer genital folds produce the labia majora. The urogenital sinus remains open to form the vestibule of the introitus (Fig. 2.9a–d).

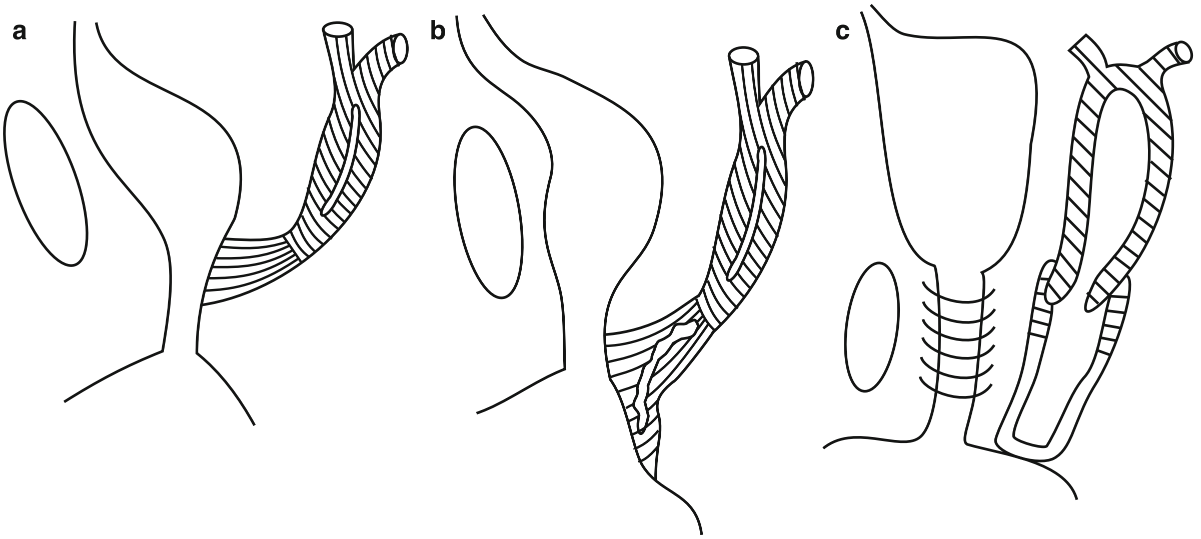


Fig. 2.5 Sagittal views of Müllerian tubercle (**a**) developing into vaginal plate (**b**), which by relative growth extends caudally to open eventually via a separate opening in the urogenital sinus to form the introitus (**c**)

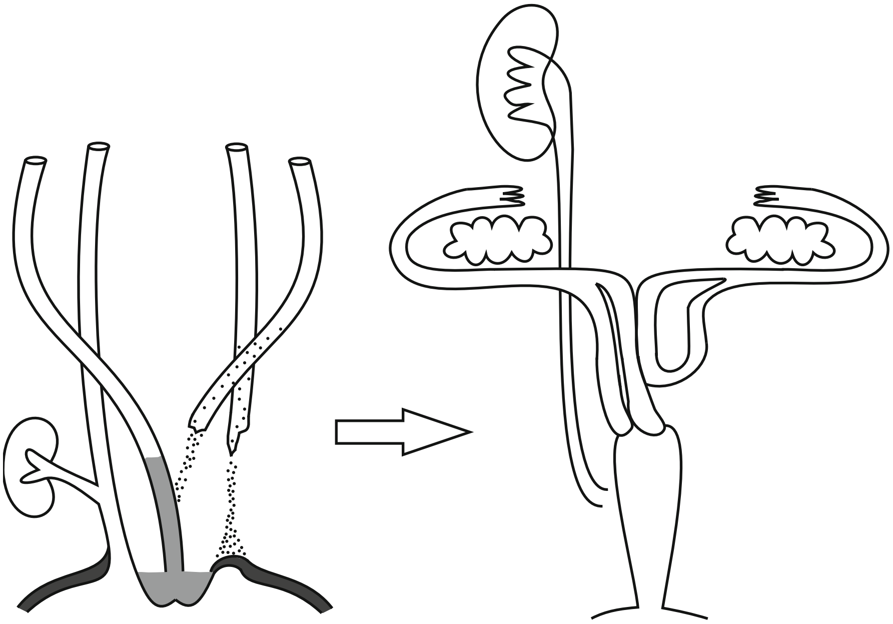


Fig. 2.6 Rokitanksy sequence. Ipsilateral failure of caudal growth of the Wolffian duct leads to absence of ureteric bud and agenesis of the ipsilateral kidney. In addition, the Müllerian duct cannot migrate caudally in the absence of the Wolffian duct as a guide, which leads to an obstructed hemi-uterus and hemi-vagina with haematometra or haematometrocolpos

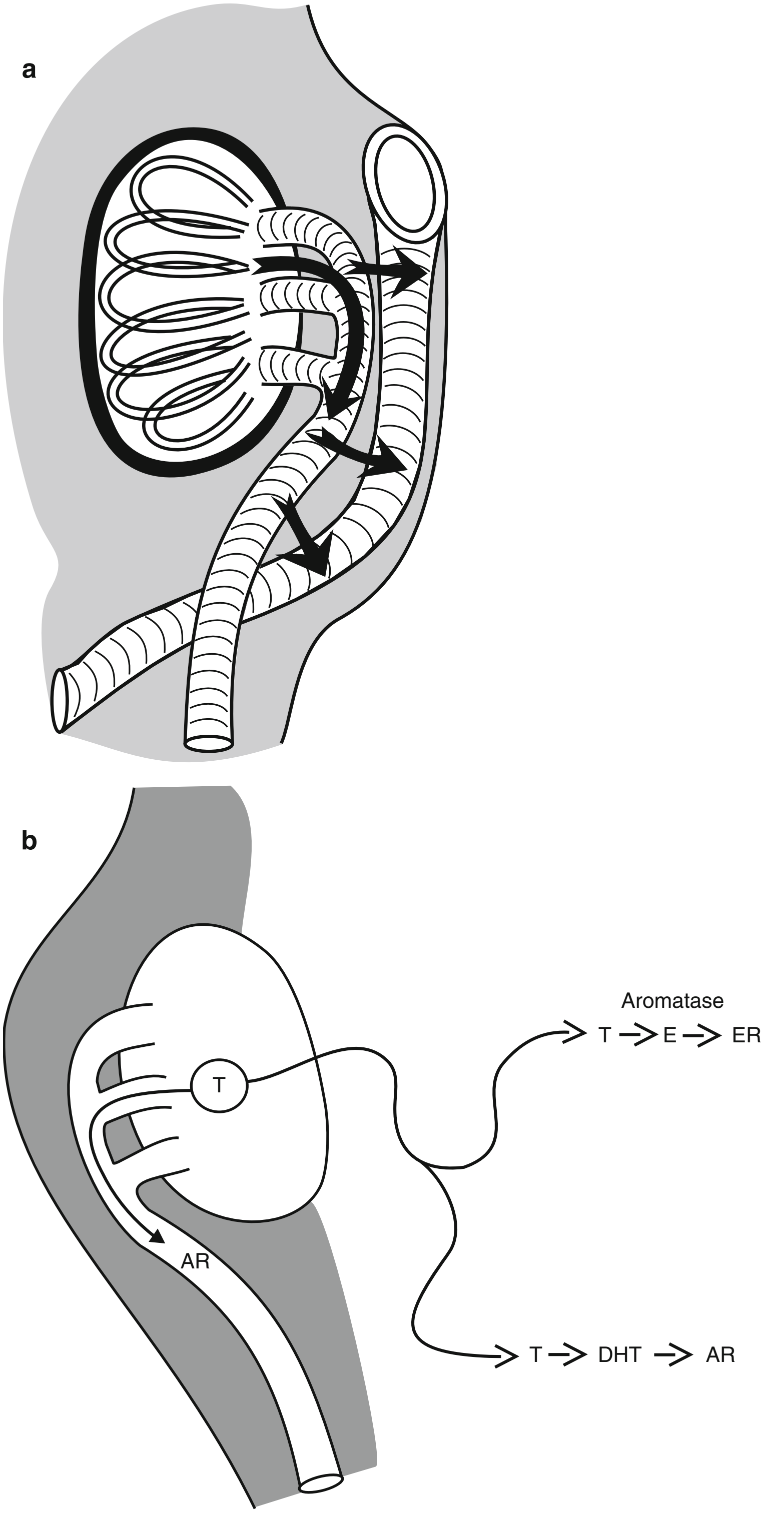


Fig. 2.7 (**a**) Schema of urogenital ridge at 8–10 weeks showing developing testis and ducts. Testosterone and Müllerian inhibiting substance (MIS/AMH) produced in the testis by Leydig cells and Sertoli cells diffuse into the duct system and pass via an exocrine manner down the mesonephric (Wolffian) duct. The testosterone is in a very high concentration which causes preservation of the Wolffian duct and its differentiation into epididymis, vas deferens and seminal vesicle caudally. Where there is gonadal dysgenesis or a block in androgen synthesis, only the cranial segment of the Wolffian duct is preserved. MIS/AMH also passes down the Wolffian duct and diffuses into the adjacent Müllerian duct to trigger regression. As with testosterone, the degree of regression is proportional to the amount of exocrine hormone reaching the duct system. (**b**) Testosterone acts by both exocrine and endocrine pathways in early development. Endocrine levels of hormone are low, presumably because the developing testis is initially very tiny, so adaptations have arisen to augment endocrine function at this stage. In some parts of the brain (in some animals) testosterone is converted to oestrogen, which then acts via the oestrogen receptor. Circulating oestrogens in females are bound to α-fetoprotein, which prevents crossing the blood–brain barrier, while testosterone can enter the brain freely. In the external genitalia and prostate the testosterone is converted by 5-alpha-reductase type-2 to dihydrotestosterone (DHT), which binds 5–10 times more tightly to androgen receptors than testosterone itself. Without this effective concentrating factor, the external genitalia cannot be masculinised by the testis, as its testosterone production is insufficient. However, at puberty, the testis is now so much larger that testosterone is capable of virilising remote tissues as the blood levels are more than 10–100 times higher than in the early foetus

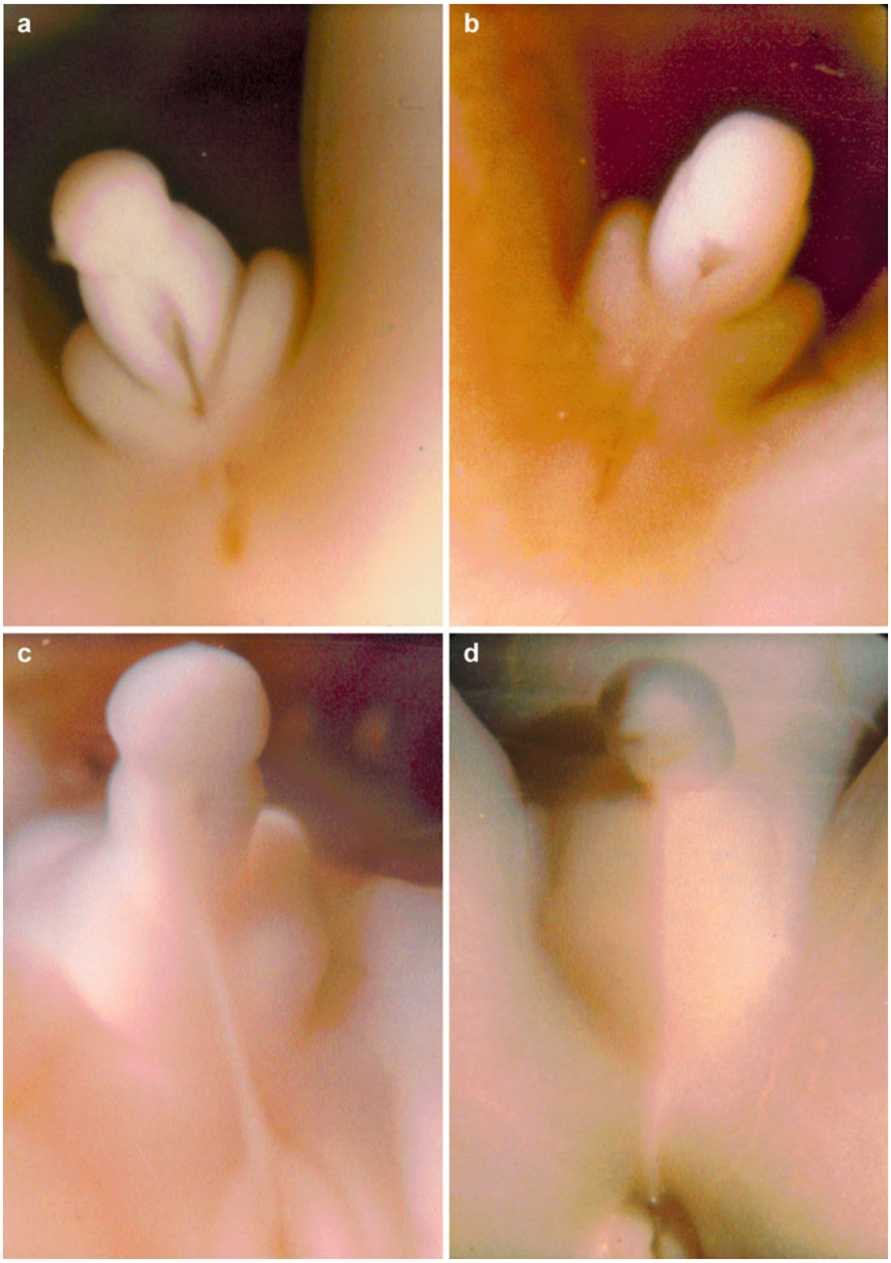


Fig. 2.8 (**a**) The external genitalia of an 8–9-week human embryo showing the ambisexual stage, just before the onset of sexual differentiation. (**b**) Transformation of the ambisexual genitalia into that of a male over 8–12 weeks. Week 9: partially fused urogenital folds. (**c**) Week 10: urogenital fusion progressing. (**d**) Week 12: fused urogenital folds. (Miller et al. 2004; Clarnette et al. 1997) (Reproduced with permission from England 1983, Clarnette et al. 1997)

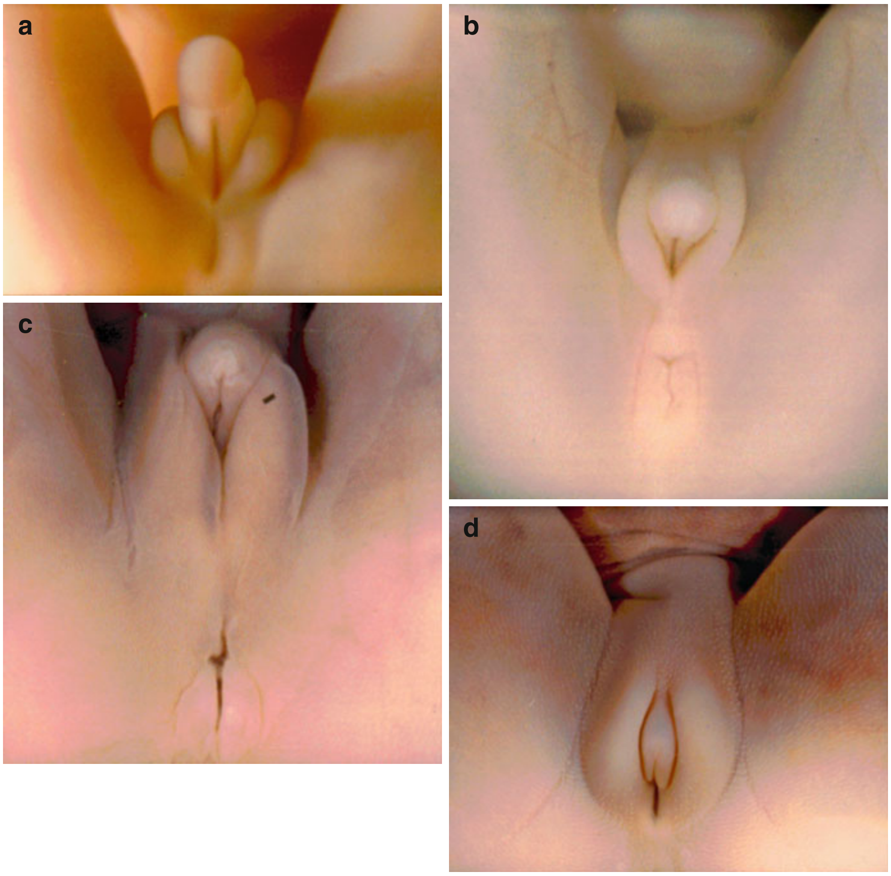


Fig. 2.9 Development of the external genitalia in female foetuses between 8 and 12 weeks. (**a**) Week 9: The clitoris is growing, but at a much slower rate than the rest of the foetus, making it look progressively smaller. (**b**) Week 13: The folding of the clitoris caused by apoptosis of the endoderm forming the urethral plate is visible. (**c**) Week 17. (**d**) Week 20. (Reproduced with permission from England 1983)

2.4 Gonadal Descent

The ovary descends relatively in the abdomen as the Müllerian ducts and their mesentery, the broad ligament, do not grow as quickly as the lower part of the abdominal cavity (Fig. 2.10). By contrast, the position of the testis is changed radically by exposure to male hormones. Between 8 and 15 weeks, INSL3 stimulates the gubernaculum to enlarge, known as the swelling reaction, which holds the testis near the groin as the abdomen enlarges. This enlarged gubernaculum in the male anchors the testis passively to the site of the future inguinal canal as the abdominal cavity grows: the passive nature of this process is probably the reason that this mechanism is rarely abnormal, and hence undescended testes inside the abdomen are rare. Around the same time, testosterone causes regression of the cranial suspensory ligament, which is the residual cranial mesentery of the urogenital ridge. In many mammals, the gonadal position is the vector sum of traction of the cranial and caudal ligaments (Fig. 2.11).

Between 25 and 35 weeks, testosterone stimulates the gubernaculum to grow out of the abdominal wall guided by the genitofemoral nerve, which releases a neurotransmitter (calcitonin gene-related peptide, CGRP) from its sensory nerve endings that provide a chemotactic gradient for the gubernaculum to follow (Hutson and Hasthorpe 2005). The processus vaginalis grows inside the elongating gubernaculum, as does the cremaster muscle. This second phase of testicular descent, requiring migration of the gubernaculum, is very complex mechanically (Hutson et al. 2010) and hence failure of this process, leading to undescended testis, is common (Fig. 2.12).

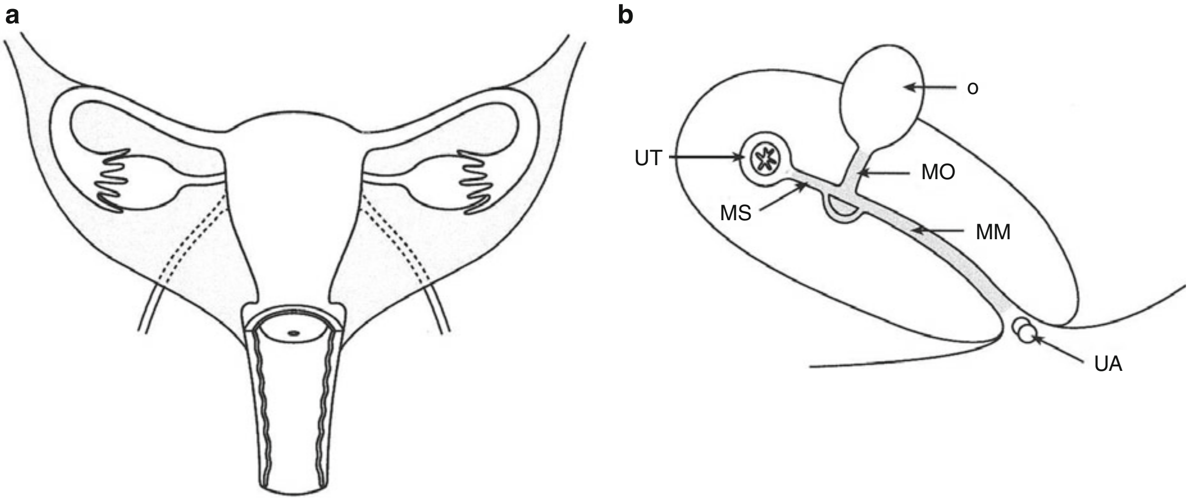
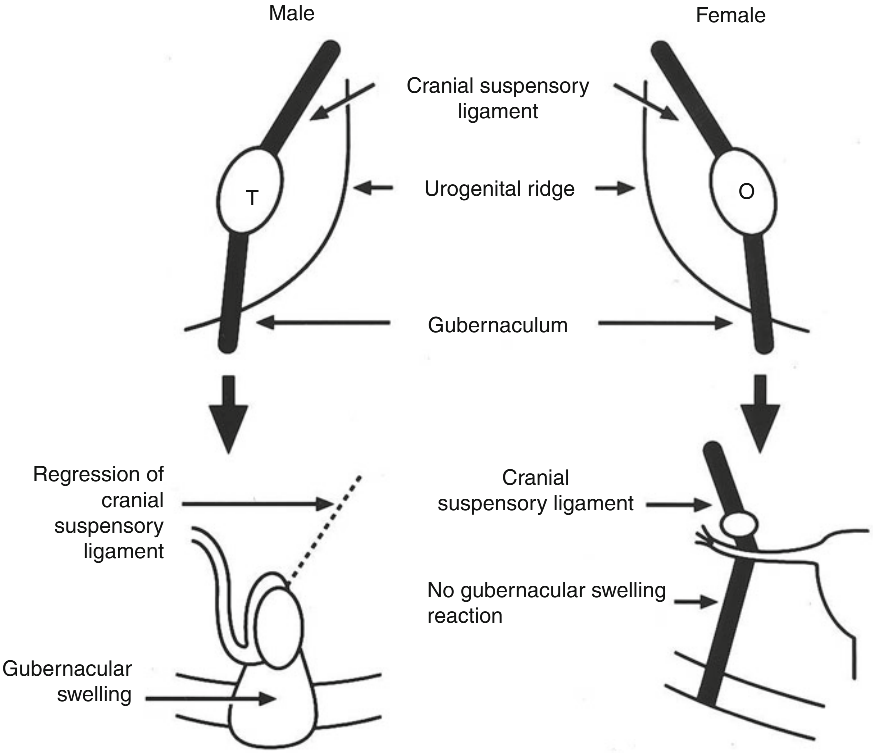


Fig. 2.10 Drawing of broad ligament (*shaded*) in adult female human shown from the back (**a**), and from the side (**b**). *UT* uterine tube, *O* ovary, *MO* mesovarium, *MS* mesosalpinx, *MM* mesometrium, *UA* uterine artery (Redrawn from Gray's Anatomy (Williams et al. 1995), and reproduced with permission from Miller et al. 2004)

Fig. 2.11 Schematic diagram illustrating the role of the gubernaculum and cranial suspensory ligaments in the final position of the gonad. In the male a combination of gubernacular swelling and regression of the cranial suspensory ligament allows the testis to remain close to the internal inguinal ring. In females the gubernaculum remains long and thin, allowing the ovary to move away from the inguinal region with growth of the embryo. The cranial suspensory ligament helps to maintain the position of the ovary on the posterior abdominal wall (Reproduced with permission from Clarnette et al. 1997)


Male
Female
Cranial suspensory ligament
T
Urogenital ridge
O
Gubernaculum
Regression of cranial suspensory ligament
Cranial suspensory ligament
No gubernacular swelling reaction
Gubernacular swelling

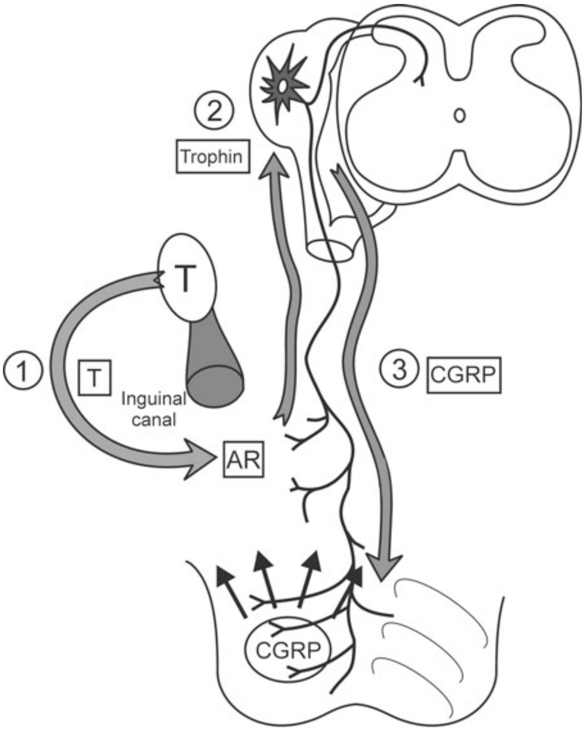


Fig. 2.12 The inguino-scrotal phase of testicular descent occurs between 25 and 35 weeks of gestation, under the control of androgen. However, the mechanism is very complex and indirect, with androgen acting mostly indirectly via androgen receptors in the inguinal region to trigger masculinisation (via an unknown trophin) of the genitofemoral nerve, which releases a neurotransmitter via its sensory nerve endings in the groin and scrotum (calcitonin gene-related peptide; *CGRP*). CGRP provides a chemotactic gradient for the migrating gubernaculum to the scrotum

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3

The Hormones Regulating Sex Development

John M. Hutson

3.1 Introduction

The hormones regulating sex development are produced by the placenta, adrenal glands and developing gonads, with some signal processing also occurring in the target organs. Androgens synthesised by the Leydig cells from 8 to 9 weeks of gestation are one of the key regulators, controlling Wolffian duct and external genital development. Müllerian inhibiting substance/anti-Müllerian hormone (MIS/AMH) is produced by the Sertoli cells and is one of the first hormones made, controlling regression of the Müllerian ducts. Insulin-like hormone 3 (INSL3) is made by Leydig cells and stimulates the swelling reaction in the gubernaculum as part of the first phase of testicular descent. Oestrogens from the foetal (or maternal) ovary have a role in differentiation of the female genital tract, but their precise role is hard to identify, as oestrogens are essential for maintaining placental (and therefore foetal) viability.

3.2 Testicular Hormones

3.2.1 Testosterone Synthesis

As in the adrenal gland, the raw material for testosterone and other steroid synthesis is cholesterol. Cholesterol enters the developing Leydig cells where it must reach the mitochondria (Warne and Kanumakala 2002). In the placenta, cholesterol can reach the mitochondria directly, but in the adrenal cortex and developing testis cholesterol needs to be actively transported across the mitochondrial membrane by steroid acute regulatory protein (StAR). The gene for this key protein is on chromosome 8p11.2, and mutations cause a rare anomaly known as lipoid adrenal hyperplasia. In this condition, steroid production is defective in both the testis and adrenal gland and accumulation of large droplets of lipid in the adrenal cortical cells leads to hyperplasia. As steroid production in the placenta is unaffected, steroid deficiency does not present until shortly after birth (with adrenal crisis in phenotypic females, regardless of XX or XY chromosomes).

Once cholesterol enters the mitochondria, its conversion to Δ^5-pregnenolone is catalysed by cholesterol side-chain cleavage enzyme ($P450_{scc}$), which is also known as CYP11A1 (Fig. 3.1). The gene for this enzyme, which also catalyses two other steroid conversions (20-hydroxylation and 22-hydroxylation) is on chromosome 15q23–24. Mutations in $P450_{scc}$ are lethal as steroid synthesis is disrupted in the placenta as well as the foetus.

Pregnenolone can be converted into either 17-OH-pregnenolone and then dehydroepiandrosterone (DHEA) by the enzyme $P450_{C17}$ (the gene is on chromosome 10q24.3), or progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD). $P450_{C17}$ also converts progesterone into 17-hydroxyprogesterone and then androstenedione at a lower level.

DHEA is converted to androstenediol by the enzyme 17β-hydroxysteroid dehydrogenase-3 (17β-HSD3), which can also convert androstenedione to testosterone and oestrone to oestradiol. Androstenediol is converted

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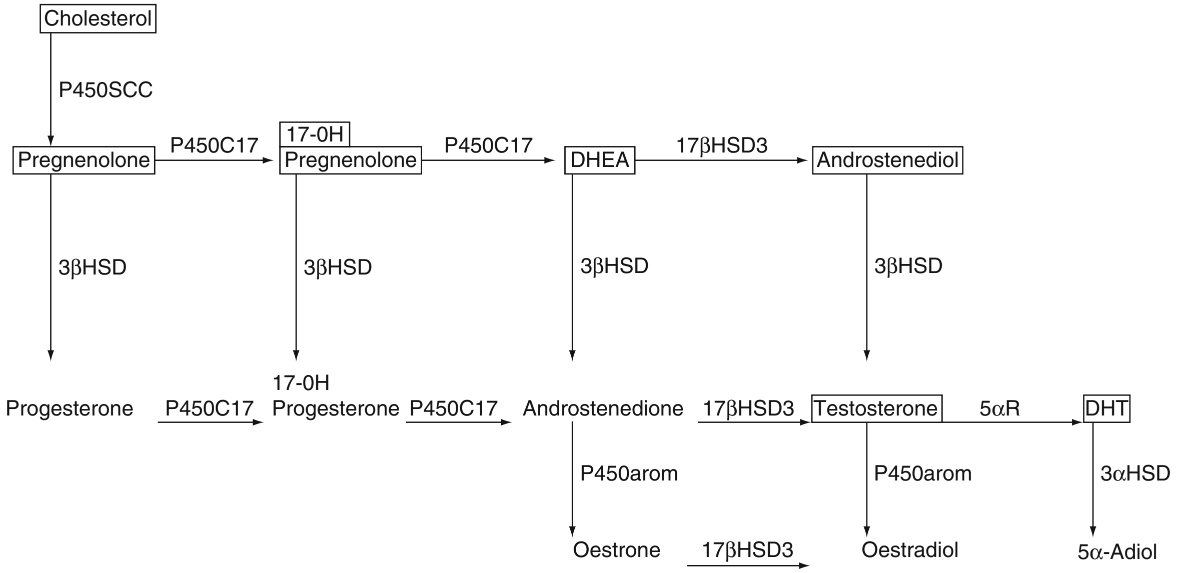

Fig. 3.1 The pathways for steroid hormone synthesis in the adrenal glands and gonads

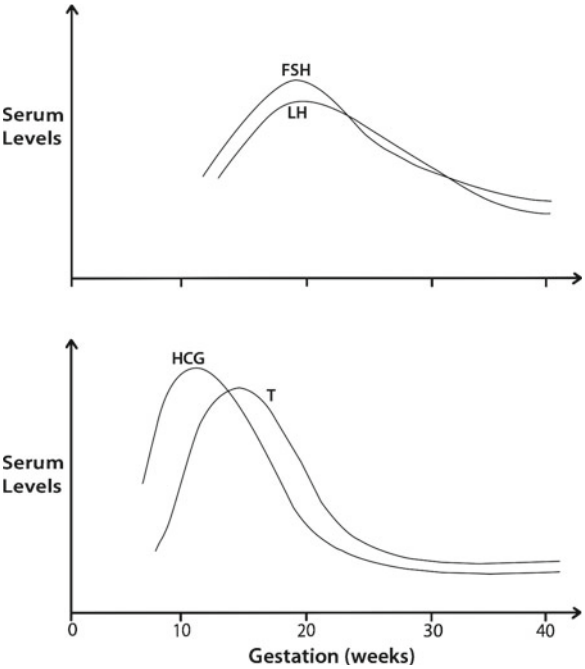

Fig. 3.2 Serum levels of follicle-stimulating hormone (*FSH*) and luteinising hormone (*LH*) (*upper panel*) and human chorionic gonadotrophin (*hCG*) and testosterone (*T*) (the *lower panel*) during gestation in a male foetus (Redrawn from Grumbach et al. (2003))

to testosterone (T) by 3β-hydroxysteroid dehydrogenase/$\Delta^5\Delta^4$ isomerase. P450 aromatase (P450 $_{\text{arom}}$) can convert testosterone into oestradiol (E_2), but a more important pathway in masculine development is conversion of testosterone to 5α-dihydrotestosterone (DHT). This binds 5–10 times more tightly to androgen receptors than testosterone itself, and allows masculinisation of the external genitalia at a time (8–12 weeks) when the blood level of testosterone is probably too low. This is because the developing testis is still too small to produce enough hormones for normal endocrine function. Mutations in the enzyme 5α-reductase-2 lead to ambiguous external genitalia at birth. However, because testosterone is secreted directly into the Wolffian duct, this is still masculinised normally. In addition, once puberty is reached, 5α-reductase-2 is no longer crucial, as the circulating blood level of testosterone is now more than adequate (because the testis is so big), and further masculinisation is common (Figs. 3.2 and 3.3).

DHT is converted by 3α-hydroxysteroid dehydrogenase (3α-HSD) to 5α-androstanediol, which in marsupials is the key androgen regulating development of the prostate, and may be the key androgen circulating in the blood (Shaw et al. 2000). It is still unknown whether this relevant for humans, but it is a theoretical cause of under-virilisation in some 46,XY DSD patients with no obvious problem in androgen synthesis.

Genital anomaly can occur in both 46,XX and 46,XY foetuses when 3β-HSD is non-functional, as testosterone synthesis is blocked in males, while DHEA has some weak masculinising effects in females.

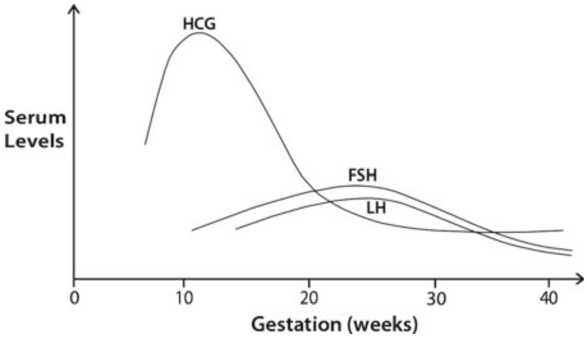

Fig. 3.3 Serum levels of human chorionic gonadotrophin (*hCG*), follicle-stimulating hormone (*FSH*) and luteinising hormone (*LH*) in a developing female foetus (Redrawn from Grumbach et al. 2003)

Mutations in 17β-HSD3 are a common cause of 46,XY DSD, and often present in teenage girls with primary amenorrhoea and signs of virilisation or palpable gonads in the groin (Boehmer et al. 1999).

Both androstenedione and testosterone can be substrates for P450 aromatase (P450 $_{\text{arom}}$), which is present in some peripheral tissues (brain, hair follicles, fat, muscle and liver), but is most active in the developing ovary and the placenta. The role of placental P450 aromatase is crucial during pregnancy, as it prevents foetal androgens in a male foetus from reaching the maternal circulation and virilising the mother. In addition it metabolises any intermediate androgenic metabolites in a female foetus to oestrogens. Mutations in the gene for P450$_{\text{arom}}$ cause virilisation of the mother as well as minor virilisation of the female foetus.

3.2.2 Androgen Receptor

The androgen receptor (AR) is a key component of the androgenic signalling pathway that is encoded by a gene with eight exons on the X chromosome. It is a member of the nuclear receptor family, which includes the steroid receptors as well as receptors for retinoic acid, vitamin D and thyroid hormone. The first exon contains a variable sequence of trinucleotide repeats associated with an adult-onset neurological disorder of spinal and bulbar muscular atrophy known as Kennedy's disease (Chamberlain et al. 1994). The second and third exons encode the DNA-binding region, which is similar in all nuclear receptors. The fourth to eight exons encode the androgen-binding region. The AR has several heat shock proteins (HSP56, 70 + 90), as well as a large number of other co-activators and co-repressors which may be linked to it, and dissociate on steroid binding. DHT has significantly higher affinity for AR than testosterone, which is probably the reason why 5α-reductase-2 has evolved in peripheral tissues such as the external genitalia, effectively increasing the concentration of androgens five to ten-fold. This concentrating effect is not needed in the Wolffian duct, as it is exposed to much higher levels of testosterone, that is secreted in an exocrine manner down the duct.

Mutations in the AR causing androgen insensitivity in the male foetus are common, as the AR is on the X chromosome, and only a single gene is present in 46,XY males (Lobaccaro et al. 1994). In addition, any anomaly of the external genitalia is readily identified, which may trigger detailed investigation. Mutations that eliminate receptor binding or function cause complete androgen insensitivity syndrome (CAIS), while some others only diminish androgen function to a variable degree, causing partial androgen insensitivity syndrome (PAIS).

3.2.3 Control of Testosterone Levels

Testosterone is first produced by the developing testes at about 8–9 weeks of development (Siiteri and Wilson 1974). However, receptors for human chorionic gonadotrophin/luteinising hormone (hCG/LH) are not found until 10–12 weeks of gestation, suggesting that initially androgen production is autonomous (Grumbach et al. 2003). Peak levels of testosterone are reached by 15–16 weeks of gestation, by which time external genital masculinisation is complete. Interestingly, this is before the foetal hypothalamic-pituitary axis is fully functional, which occurs about 15 weeks of development. After the peak of testosterone levels at 16 weeks, the serum level falls to about half (3.5 nmol/L) until about 24 weeks, after which it is lower but still measurable.

The serum levels of foetal testosterone mirror that of hCG, suggesting that the placenta has an important role in the early events of male sexual development (Kaplan et al. 1976). The key masculinising effects during the second half of gestation (i.e. growth of the penis and scrotum and testicular descent) are probably regulated by the foetal hypothalamus, as babies with congenital hypopituitarism and anencephaly have normal early masculinisation, but micropenis and hypoplastic scrotum with cryptorchidism (Grumbach et al. 2003). With the success of perinatal paediatrics, we now see extremely premature infants with severe intrauterine growth retardation (IUGR), and inadequate masculinisation of the external genitalia in these baby boys is consistent with inadequate placental hCG to stimulate testosterone production from the foetal Leydig cells during a critical phase of sex development.

3.2.4 Müllerian-Inhibiting Substance/Anti-Müllerian Hormone (MIS/AMH)

This is a large glycoprotein (140 kDa) secreted by developing Sertoli cells and is one of the first substances produced by the differentiating testis. MIS/AMH is secreted into the Wolffian duct and diffuses into the adjacent Müllerian duct to trigger its regression. Identification and purification of MIS/AMH took nearly 40 years after Alfred Jost first proposed that there must be another testicular hormone apart from testosterone involved in male sexual differentiation.

MIS/AMH is secreted by the testis from 8 to 9 weeks of gestation and post-natally there is an increase in secretion coincident with ‘minipuberty’ at 3–12 months, after which the blood levels decline but remain measurable until the onset of puberty (Yamanaka et al. 1991). After puberty MIS/AMH is very low in the bloodstream in males, but still measurable in the semen (where its function remains unknown).

In females the granulosa cells of the ovary produce MIS/AMH but secretion does not begin until well after sexual differentiation is complete, around the time of birth (Seifer and MacLaughlin 2007). During the ovarian cycle, MIS/AMH has an important but as yet ill-defined role in follicular physiology.

The *MIS/AMH* gene contains 5 exons and is located on chromosome 19. The signals controlling activation of the gene at the onset on sexual differentiation are under active analysis, with *SOX9*, *SF1*, *WT1* and *GATA4* known to be involved. There is keen interest in this area, because MIS/AMH is one of first secreted factors to be produced after activation of the SRY gene in developing males (see Chap. 1 for details).

MIS/AMH acts via two receptors, AMHR-1 and AMHR-2. The ligand binds to AMHR-2, which is a transmembrane serine/threonine kinase, which then phosphorylates the type-1 receptor. The active unit is a tetramer of two molecules each of the type-1 and −2 receptor, which on MIS/AMH binding initiates an intracellular signalling cascade leading to gene activation. Regression of the Müllerian duct occurs in a cranial-to-caudal wave of apoptosis as MIS/AMH diffuses down the urogenital ducts at the same time that the distal Müllerian duct is still migrating to the cloaca.

Anomalies in the *MIS/AMH* gene or its receptors cause persistence of the Fallopian tubes, uterus and upper vagina in males (Josso et al. 1983). In mice with homozygous deletion of *Mis/Amh* the Wolffian ducts become obstructed by persistence of the Müllerian ducts, leading to infertility. In addition, the Leydig cells show hyperplasia (Josso et al. 2001). Over-expression of human *MIS/AMH* in mice causes loss of the Müllerian ducts in females and inadequate virilisation in males, secondary to suppression of steroidogenesis in the Leydig cells (Behringer et al. 1990).

Humans with mutations in *AMH* or *AMHR-2* show a similar, but not identical phenotype. Boys with this rare anomaly, known as the persistent Müllerian duct syndrome (PMDS), have normal virilisation of the external genitalia but abnormal descent of the testes. By contrast, in the rodent testicular descent is normal. The cord of the gubernaculum in humans with PMDS is elongated so much that it resembles an elongated round ligament in a female. This suggests that MIS/AMH has an important role in gubernacular development and testicular descent, at least in humans. The absence of obvious morphological effects of MIS/AMH mutation in the rat gubernaculum, despite the presence of amhr-2, suggests that MIS/AMH has only a minor role in gubernacular development in the rodent. Cryptorchidism in humans with PMDS has been postulated to be secondary to mechanical effects of the retained uterus (Josso et al. 1983), although the abnormally long gubernacular cords and mobility of the internal genitalia does not support this (Hutson and Baker 1994). Indeed, the excessively mobile testes appear to be at a higher risk of prenatal torsion, causing the vanishing testis (Imbeaud et al. 1995).

3.2.5 Insulin-Like Hormone 3 (INSL3)

It was known for many years that the swelling reaction in the rodent gubernaculum was caused by a low molecular weight factor, but it remained unidentified until 1999. The missing hormone was called 'descendin' (Fentener van Vlissingen et al. 1988). The mystery was eventually solved from another part of biology, when transgenic mice were generated with mutations in a gene related in structure to insulin and relaxin. The mutated male mice had intra-abdominal testes with absence of the swelling reaction in the gubernaculum, supporting the proposal that so-called descendin was actually insulin-like hormone 3 (INSL3), also known as relaxin-like factor (RLF) (Nef and Parada 1999; Zimmermann et al. 1999).

INSL3 is partly homologous with relaxin, consistent with both hormones evolving from a common precursor gene. Duplication of this ancestral gene occurred about the time of early mammalian evolution, with relaxin becoming involved in breast development and INSL3 acting on the gubernaculum (Park et al. 2008). INSL3 and relaxin have separate receptors (LGR8 and LGR7 respectively), but with some overlap in binding between alternate ligands and receptors.

A mutant mouse with a partial chromosomal deletion (GREAT) was identified with a similar phenotype to INSL3 mutant mice, and was subsequently found to have a deleted LGR8 receptor (Gorlov et al. 2002). The INSL3 receptor (LGR8) has been localised to the foetal gubernaculum (Park et al. 2008), and addition of synthetised human INSL3 to rat gubernaculum in organ culture caused the expected swelling reaction (Kubota et al. 2002). Auxiliary roles were found for dihydrotestosterone (DHT) and MIS/AMH, and the AMHR-2 receptor was also present in the gubernaculum, along with LGR8, but not LGR7 (Kubota et al. 2002).

Release of INSL3 from the foetal Leydig cells occurs at the time of the swelling reaction during the first phase of descent (10–15 weeks in humans), but the regulation of its secretion is not yet known. MIS/AMH may play a role, as there are AMHR-2 receptors on Leydig cells, and transgenic mice with over-expression of MIS/AMH have interference with Leydig cell function. MIS/AMH is quite likely to have a more significant role in humans, as compared to rodents, as evidenced by the abnormally long gubernacular cord in boys with PMDS (Hutson et al. 1987, 1994).

3.3 Ovarian Hormones

Oestrogen synthesis is possible in the developing ovary, even as early as 8–9 weeks of gestation (George and Wilson 1979). However, the cell within the early ovary that can synthesise oestrogen may well be an interstitial cell, rather than the granulosa cells, which are not yet fully formed (Gondos and Hobel 1973). There are no gonadotrophin receptors in the early ovary between 8 and 16 weeks of development, so that the foetal ovary becomes sensitive to gonadotrophins between 16 and 20 weeks of development, which is probably important for the later development and maintenance of the ovarian follicles (Grumbach et al. 2003).

The role of oestrogens in development of the female genital tract remains difficult to determine, as models of oestrogen deficiency are not compatible with pregnancy. It is quite likely that both maternal oestrogens, along with foetal ovarian oestrogens in the second and third trimester have key (as yet unidentified roles) in uterine and vaginal differentiation.

3.4 The Placenta

The placenta has several key roles in sex development. Chorionic gonadotrophin (hCG) is the likely main regulator of testosterone production during the crucial phase of sexual differentiation between 8 and 15 weeks, when the internal and external phenotypes are modified. Later in gestation this regulatory function is mostly taken over by the foetal hypothalamic-pituitary axis, which oversees gonadal hormone production to allow penile and scrotal growth, as well as testicular descent, in males, and uterine and vaginal development in females.

Another key placental function is to aromatise any gonadal or adrenal androgens in the foetal bloodstream, thereby preventing masculinisation of both the mother and a female foetus (Grumbach and Auchus 1999).

3.5 The Foetal Hypothalamic-Pituitary Axis

Development of the male genitalia requires a functional hypothalamic-pituitary-gonadal axis, but only in the second half of pregnancy, after sexual differentiation of the external genitalia is complete about 12–15 weeks of

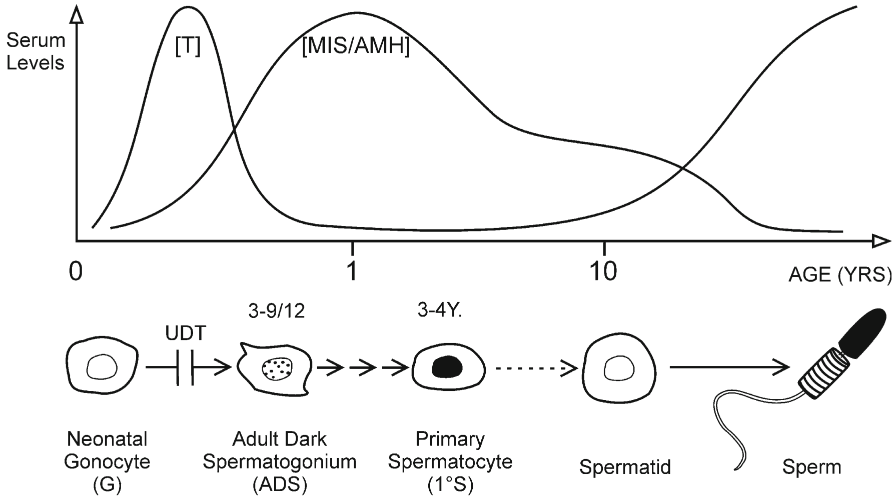

Fig. 3.4 Schema of serum levels of testosterone (*T*) and Müllerian inhibiting substance/anti-Müllerian hormone (*MIS*/*AMH*) from birth to puberty, along with the testicular germ cell development. Note the hormone peaks in the first year and the block in germ cell maturation from gonocytes to adult dark spermatogonia caused by undescended testes (*UDT*)

gestation. Initially, androgen production is autonomous, but is probably quickly brought under the control of placental hCG. Baby boys with hypothalamic or pituitary disorders have no ambiguity of their external genitalia, but show inadequate phallic growth with micropenis, and scrotal hypoplasia and cryptorchidism. Since the first phase of testicular descent is controlled by INSL3 stimulating the swelling reaction in the gubernaculum, the testes are nearly always descended to the inguinal region where they are palpable just outside the external inguinal rings.

3.6 Post-Natal Hormone Levels and Implications

Shortly after birth in a baby boy, the serum levels of androgens and MIS/AMH fall to basal levels, so that within a week or two they are barely detectable. However, at 2–3 months of age a surge of gonadotrophins triggers a sudden rise in testosterone production, so that between 3 and 6 months of age the serum levels are similar to those in adolescent boys. This transient peak in androgen levels is known as 'mini-puberty', and there is speculation that it is important for early postnatal germ cell development (Hadziselimovic et al. 2007). We have also suggested that it may be required for ensuring complete obliteration of the processus vaginalis to prevent inguinal hernia development (Clarnette et al. 1997). An even more intriguing possibility is that this postnatal androgen surge might be involved in the final steps in the pathway towards gender identity. There is no direct evidence for this in humans, but in other mammals and birds there is good evidence that that this short burst of androgens is not only present, similar to humans, but also crucial for subsequent masculine behaviour in the adult animal (Hrabovszky and Hutson 2002). If this turned out to be true in humans then we would need to take this into account when managing babies with DSD. Like testosterone, there is also a postnatal rise in MIS/AMH, but this occurs slightly later at about 6 months, it then reaches a peak at 12 months, but remains high throughout childhood, not falling again until the onset of puberty (Fig. 3.4) (Baker et al. 1990; Baker and Hutson 1993). Even less is known about the possible functions of MIS/AMH than testosterone, but there is speculation that it may also have a role in germ cell development (Zhou et al. 1993). More research is needed to understand the place of post-natal hormones in sex development, as it quite likely to have important clinical implications.

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Questions About Gender: Children with Atypical Gender Development

4

Louise Newman

4.1 Introduction

Gender dysphoria – the sense of discomfort or disease with one's biological sex and assigned gender role – may present in children from the age of 2 years. This may have a significant impact on child development in a broad way and also on family functioning. Families vary in their response to a child's cross-gendered preferences or gender questions with some showing acceptance and tolerance and others expressing anxiety and a desire to resolve the issue. There are scarce data available as to the prevalence of this condition in children and there is ongoing debate about the best clinical approach. The evidence base about treatment in children is limited and the ethical issues are complex. It is essential when seeing children with gender issues to try and understand the families' ideas and expectations around sex differences and appropriate gendered behaviour and the way in which these ideas impact on their relationship with their child. The child with atypical gender development faces not only the dilemma of lack of congruence between body and psychological gender identification but also the anxiety that this issue often arouses in parents and carers. Supporting children with gender variance involves family counselling, individual work with the child and attention to the school environment. The use of hormonal interventions around the time of puberty remains controversial but can relieve distress in children with ongoing gender dysphoria and support psychological interventions.

4.2 Concepts of Sex and Gender

The anatomical sex of an infant and parents' own ideas and values about gender and behaviour are key aspects of early parenting. Parents will have a range of views about gender which influence interaction with the infant and parenting expectations.

Theories of infant development have tended to focus on 'sex differences' as opposed to gender development. More recently, interests have turned to understanding the complex interactions of biology and social experiences or culture that are involved in creating gender.

Concepts of sex and gender exemplify the tensions between biology and culture, and old and newer models of development. In older models, sex is usually seen as genetically influenced and innate and results in psychological or social differences in males and females or gender roles. Contemporary theories point out that biology always interacts with environment. Biological sex differences are influenced by culture and language and differing social expectations of males and females. Cultural expectations also influence parenting and the earliest interactions with male and female infants.

4.2.1 Biological Sex and Infant Development

The majority of neonates are designated either male or female at birth, or prenatally with the use of ultrasound technology. Biological sex has profound implications for infant development for complex reasons. First, there is increasing evidence of differences in male and female brain differentiation, although the extent to

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which this directly influences observable sex differences in behaviour and psychological functioning is unclear. Second, caregivers have their own sets of beliefs and expectations about male and female infants, which influence their perceptions of and interactions with their infants. Finally, different social and cultural groups have complex and variable expectations and definitions of masculinity and femininity, which define appropriate behaviours, personality attributes and social roles. These definitions change over time. Infants develop a sense of gender identity or a self-definition as male or female in the first 2–3 years of life, and this is influenced by biological, psychological and socio-cultural factors. There are ongoing debates over the relative importance of these factors in producing observable differences between males and females but it is clear that differences are evident in infancy.

4.2.1.1 Definitions

Contemporary theories distinguish sex from gender:

Sex refers to anatomical and biological (genetic and hormonal) categories of male and female, but even biology is complex and subject to interpretation. In nature, there may well be more than two sexes or at least variability in male and female sexual characteristics.

Gender refers to a prevailing socio-cultural model that defines social expectations of masculinity and femininity. These expectations encompass socio-cultural models of personality, attitudes and behaviours that are seen as linked to each sex. Gender also refers to the social performance indicative of an internal sexual identity – the outward behaviours of masculinity or femininity as they are socially defined.

Gender identity is a complex mixture of biology, socialisation, psychological identification and sexuality. It refers to the individual's sense of himself or herself as a biological, psychological and social male or female. There is ongoing discussion about the neurobiological basis for gender-identity.

Gender role refers to the behaviours, attitudes and personality traits designated socio-culturally as masculine or feminine. Gender role is incorporated in the self as a set of behaviours, attitudes and personality traits designated socio-culturally as masculine or feminine. In children, this is measured by such variables as affiliative preference for same-sex peers, fantasy and play roles and type of play. There is an ongoing controversy over the influence of biological variables such as prenatal sex hormones on observable gender-role behaviour.

Sexual orientation is defined by response to sexual stimuli while sexual identity refers to the definitions of oneself in terms of sexual preference. Sexual orientation emerges after puberty but is not necessarily congruent with sexual identity. For example, it is possible for a male to be primarily aroused by homosexual stimuli but to have a gender identity of himself as a heterosexual.

4.2.1.2 Disorders of Sex Development

Deviations in the normal steps of sexual differentiation can result in so-called disorders of sex development (DSD) with disruption of internal and/or external sexual structures. There are a variety of conditions some with unusual external genitalia and others with poorly developed internal sexual structures. Some neonates have 'ambiguous genitalia' most commonly masculinisation of the external genitals of a female infant due to exposure to male hormones *in utero* where an excess of androgen is produced by the adrenal gland (i.e. congenital adrenal hyperplasia [CAH]). Other conditions include ovo-testicular DSD, and complete androgen insensitivity syndrome (CAIS) – a condition where a 46,XY infant has female external genitalia.

The clinical question involved with DSD is how to decide to what sex the infant should be assigned. Money and Ehrhardt (1968) studied the rearing of DSD children in the 1950s, and concluded that sex of rearing – upbringing – was the most important factor in producing a 'successful' outcome as male or female. They also stated that attempting to change gender after the age of 2.5 years was not likely to be successful. More recently this has been challenged by the concept of 'brain sex' and the biological factors underlying gender identity.

Example: Mary

Mary, aged 2 years, was born with multiple pelvic abnormalities, including an imperforate anus, ambiguous external genitalia with penile agenesis, and urinary system abnormalities. Examination of chromosomes showed the infant to be 46,XY and an ultrasound examination showed internal undescended testes. Mary needed emergency surgery to the urinary system and bowel and was raised as female having later genital surgery. At 2, Mary is a secure child with female appearance who enjoys 'female-type play' but also 'rough and tumble' activities. While there is some evidence that male and female brains develop differently in utero, socialisation is a very important influence on gender identity.

4.2.1.3 Caregivers' Beliefs and Expectations

Core gender identity was defined by Stoller (1968) as the fundamental sense of belonging to one sex. This is an emotionally valued sense of identity and develops between the ages of 18 months and 3 years. This process will be affected by biological factors and the infant's interactions with carers. For both male and female infants, the first experience of intimacy and sexual feelings is with the primary carer. Within the family, the infant learns about the experience, expression and control of sexual feelings, and about sexual difference. The attitudes of carers about sex, sexuality and gender will have a significant effect on the child's gender development. Infants appear to develop a sense of their own gender and an understanding of gender as a fundamental aspect of the self and others in three stages:

Gender labelling: From about 18 months, the infant is able to label individuals as male or female according to external appearance. They do not see gender as fixed, and if appearance changes, they think gender may have changed.

Gender constancy: By 3 years of age, gender is part of the self-concept. The child is interested in same-sex peers and activities. They are aware that changing appearance or activity does not change gender.

Gender stability: By 4–5 years, gender is seen as an unchangeable, stable attitude of the self and others.

According to psychoanalytic theorists, such as Fast (1984) and Stoller (1968), the acquisition of gender identity occurs as a component of separation and individuation and the development of self-identity. The attachment relationship is the context in which sense of identity and gender identity both develop.

Social and Cultural Expectations

In the West, gender is used to distinguish socially constructed roles and cultural representations from biological sex. What we call gender is seen as social, and biological sex is seen as its point of origin and natural limit. In this model, gender should conform to sex.

4.2.1.4 Cultural Variance in Attitudes Towards Gender

Anthropological and sociological studies have identified significant cultural variation in gender systems and attitudes towards gender variance. Wide variations exist in beliefs about the nature of biology and what constitutes sex, and physical difference per se is not always seen as sufficient to produce gender. The Zuni tribe of North American Indians, for example, do not allocate sex at birth regardless of the appearance of external genitalia, as there is a belief that it may change. Complex rituals are used to 'discover' the sex of the infant and determine sex of rearing. In this situation culture is used to 'interpret' biology that is not self-evident and is not automatically linked to gender identity (Lacquer 1990).

In some cultural contexts, ambivalent and non-stable gender roles and identities are accepted and not necessarily seen as pathological or disordered. It is possible for gender to be neither male nor female, and for gender transformation to occur well after the age in which psychoanalytic and social learning models would see it as 'irreversible' (Herdt 1994). The most studied example of culturally understood gender change is the 'penis at 12' syndrome in the Dominican Republic and equivalent conditions in Papua New Guinea and the South Pacific. In these examples, children with an enzymatic deficiency (5α-reductase type-2 is unable to convert testosterone to DHT) are born with ambiguous external genitalia and raised in many cases as female. Virilisation (that is, the activation of the androgenic pathways by excess testosterone, bypassing the need in the fetus for DHT) may occur at puberty and many 'change gender' and successfully adopt a male identity. This change is usually unproblematic and this may well reflect the social acceptance of the phenomenon and challenges the concept of a fixed and unalterable 'core gender identity' (Stoller 1968).

Similarly, the social acceptance and position of gender-variant individuals shows great cultural variation. Among North American Indians, cross-gendered individuals known as Berdaches have been documented in over 150 groups. Berdaches are assigned a position of high social status within a spiritual system and are seen as a 'third gender', transcending male and female categories. In several religious traditions, deities are seen as hermaphroditic or capable of gender change, which enhances rather than diminishes spiritual power. In the Hindu tradition, for example, the Lord Krishna frequently changes sex and male transvestism is used in Tantric devotions. The Hijras of contemporary India are a diverse group of ceremonially castrated males, intersex individuals and 'feminine males' and are again seen as 'alternative' genders within the Hindu context (Newman 2002).

4.2.1.5 Significance of Cultural Variations

The significance of these cultural variations is that they raise the possibility of alternative models of the relation between sex and gender and suggest that there is no fixed relation between the body, psychological identification and the social manifestations of gender. It has also been argued that cultural context determines whether gender variation is seen as a ‘disorder’ needing treatment or an understood and tolerated variation. For the clinician it is important that adoption of a Western model and formulation of gender identity and development does not preclude an understanding of possible alternative frameworks, and a particular normative model of gender development is not rigidly imposed on children and families seeking to understand gender variation.

It is clear that whether or not gender variability is seen as a mental disorder is strongly influenced by cultural expectations of gender behaviour. What is seen in one culture as problematic may not be seen in the same way by another culture. The important consideration is whether concerns about gender behaviour have an effect on the infant’s social relationships and functioning.

4.3 Clinical Presentations

No reliable data exist for estimating the incidence of gender dysphoria and gender-identity disorder (GID) in the general population. Boys are referred more than girls (ratio of 5:1) but it is not clear if this is the result of greater tolerance of gender variant behaviours in young girls, and a corresponding social anxiety about so-called effeminate boys. Longitudinal studies suggest that not all childhood gender dysphoria is associated with a trans-sexual outcome (Zucker 1995) and there are ongoing discussions about the relationship of childhood gender dysphoria and adolescent and adult-type cross-gender identification and trans-sexuality. It is possible that there are several developmental pathways to the growth of cross-gendered identification in children and that this is not a unitary condition. As discussed below, neurobiological theories tend to see gender as an outcome of brain functioning, whilst psychological theories have focused on early development of identity within the context of attachment relationships and see gender issues arising in this context.

Regardless of aetiology children with gender dysphoria present with a range of cross-gendered fantasies and behaviours and show preference for games, activities and clothes usually assigned to the opposite sex. Young boys around 2–3 years of age may be interested in persistent cross-dressing and are very attentive to details of female fashion, behaviours and mannerisms. Little boys may show clear preference for playing with girls and prefer dolls and home themes in play. They identify with female characters in stories and film and prefer characters such as Cinderella or Snow White. They show little interest in boy-type activities or typical rough-and-tumble play. The play is usually persistent and difficult to discourage. Older boys may make more direct statements regarding their desire to be a girl or experience of ‘really being’ a girl in a boy’s body. The majority of boys are aware of their anatomical sex but feel it is incorrect or a mistake and some develop marked aversion to their genitals and attempt to hide them.

In girls the presenting issues are very similar with young girls identifying with male activities and behaviours and often expressing the belief that they will grow a penis in the future. At school they prefer to play with boys and may insist on going to the boy’s bathroom and wear boys’ or gender-neutral clothes. They experience distress if they are made to wear girls’ clothes or join in girls’ activities such as games.

Clearly these experiences can be confusing and distressing for the child who immediately has a sense of difference from their peers. Young children might express their confusion openly but in the face of teasing or bullying have a sense of a secret that could be potentially dangerous. Whist some children confide in parents and family, families themselves are often confronted and confused by their child’s issues and may also experience anxiety about how the extended family and community will respond.

4.4 Diagnostic Classification

The diagnosis of GID remains controversial. The DSM IV (American Psychiatric Association) criteria refer to a strong identification with and preference for the gender role characteristics of the other sex (Table 4.1).

4.4.1 Differential Diagnosis

In young children around 2.5–3.5 years of age gender becomes part of self-definition and the social world.

Table 4.1 Diagnostic criteria for Gender Identity Disorder (GID)

A. A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex)

In children, the disturbance is manifested by 4 (or more) of the following:

1. Repeatedly stated desire to be, or insistence that he or she is, the other sex
2. In boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing
3. Strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex
4. Intense desire to participate in the stereotypical games and pastimes of the other sex
5. Strong preference for playmates of the other sex

In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex

B. Persistent discomfort with his or her sex or the inappropriateness of the gender role of that sex

In children, the disturbance is manifested by any of the following: in boys, assertion that his penis or testes are disgusting or will disappear, assertion that it would be better not to have a penis, or aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities; in girls, rejection of urinating in a sitting position, assertion that she has or will grow a penis, assertion that she does not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing

In adolescents and adults, the disturbance is manifested by symptoms such as pre-occupation with getting rid of primary and secondary sex characteristics (e.g. request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex

C. The disturbance is not concurrent with a physical DSD condition

D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

The child can label self and peers according to gender by around 28 months (Fagot 1995) and this is related to the development of same-sex play preference. In typical development gender becomes integral to a positive self-concept.

Prior to this it is common for young children to express the wish to be 'all sexes' and to have the characteristics of both genders. A small boy for example may wish to give birth or grow breasts and still remain a boy, and a girl may wish to grow a penis. The wish to be both genders is generally given up but may be accompanied by anger and envy. This should not be seen as GID where the wish is to be the opposite sex and there may be aversion to the assigned sex.

It is also important to look at the context of development of cross-gender interests and wishes as transient wishes may occur in the context of anxiety particularly as this relates to the mother as primary attachment figure. In some cases the child may be anxious about the availability of the mother and seeks comfort in adopting a female role, in other cases the child may be anxious about the mother's acceptance of their gender. This may occur for example if the mother has experienced trauma or assault by a male figure. These dynamics can impact on the child's experience of gender and may represent unresolved issues relating to gender and sexuality in the mind of the parent. It is significant that studies find an association between GID and maternal depression and anxiety in the child's first 3 years of life (Zucker 1995).

Assessment of the child and family should also examine the family and cultural understanding of gender behaviour and attitudes towards gender non-conformity. Some families react with anxiety if a boy shows typically female interests and this may relate to an underlying anxiety about potential homosexuality. There is cultural variation in tolerance for cross-gender behaviour which influences both family response and presentation of treatment (Newman 2002).

4.5 Theories of Atypical Gender Development

It is likely that there are several developmental pathways to GID in childhood and that not all childhood GID is related to trans-sexuality in adulthood. Both psychological and biological models of the condition have been proposed and these may well be describing somewhat different conditions. Biological theories have focused on processes of brain sexual differentiation as male or female and the influence of pre- and perinatal sex hormone exposure. It is proposed that there can be a discrepancy between genital differentiation and brain sex differentiation underlying trans-sexuality presumably resulting in early-onset cross-gender identification.

Other models have examined sexually dimorphic brain nuclei in the hypothalamus which are hypothesised to influence gender identity and sexual orientation. Small studies of the brain of male-to-female trans-sexuals have reported small volumes within the range of typical females (Zhou et al. 1995) and the opposite can be found in a female-to-male case. These findings, whilst interesting, do not however amount to a direct endorsement of possible mechanisms for this difference. Current psychological theories look at vulnerabilities for the development of GID along with factors in parenting and attachment that may shape the development of gender dysphoria. Coates and Person (1985) describes GID boys as having temperamental anxiety and vulnerability to separation as well as common trauma in the relationship with the mother in early childhood including maternal depression and family disruption or conflict. She proposes that the child experiences separation anxiety and identifies with the mother to avoid losing her.

Zucker (1995) also argues that children with GID may be predisposed to anxiety and that this is exacerbated in the context of an insecure attachment relationship. They note that some families may reinforce cross-gender behaviour and interests and those particular aspects of the parents' gender issues influence their response to the child. For example, mothers with issues related to masculinity and a perception of male aggression may be less rewarding of typical male behaviours. Fathers in some families have been described as distant and not providing positive male role models for boys with GID.

Several studies have found significant rates of psychological disorder in parents of children with GID including personality disorder, maternal post-natal depression and indications of maternal emotional unavailability (Marantz and Coates 1991). These however are very general factors associated with a range of attachment issues and mental health or developmental outcomes and cannot be seen as providing a specific model of the development of GID.

Table 4.2 Issues in cross-cultural assessment of GID

A. How does the culture understand the differences between male and female?
B. What account is given of the development of male and female individuals? Are differences and roles 'innate' or 'learned'?
C. Are all individuals male or female, or are alternative positions possible?
D. What does the religious/spiritual context say about gender roles and positions? Are there taboos against the violation of gender roles and gender change?
E. Does the culture separate questions of sexual orientation from gender, or is gender variation seen as signifying potential homosexuality?
F. What are the cultural attitudes towards homosexuality and gender variation?
G. Does the culture have an assigned place for gender-variant individuals?
H. What attitudes exist about sex-modifying procedures and the involvement of medical/surgical systems in interventions aimed at gender change?

4.6 Assessment Issues

Increasingly there have been challenges to both the notion of a purely socio-cultural construction of gender identity and to the idea that binary biological sex determines psychological aspects of gender. This increasing complexity points to the need for a bio-psychosocial understanding that can take into account interactions between biological and psychosocial factors in mediating gender identity.

In clinical practice and assessment of children with gender dysphoria and their families these debates are frequently a focus of discussion. Parents are often focused on supporting their child and react in a protective way. Some parents support a biological model of aetiology and find exploration of other factors difficult. Initially it is important to explore the families' particular understanding of gender and gender variance and how this may be influenced by cultural belief systems. Table 4.2 lists issues in cross-cultural assessment of GID.

4.6.1 Cross-Cultural Assessment

A major issue in the assessment of gender dysphoria in multicultural contexts is how best to establish the particular model of sex-gender and gender deviance held by the child and family. Planning appropriate intervention can only occur when it is seen how the family understand gender variation and how it will be managed within the cultural framework of the family. It is also important that the child be supported in his overall social context and in managing what may be a 'cultural gap' between the family and mainstream social values.

The following examples illustrate some of the complexities of cross-cultural assessment.

> Example 1: Michael
> *Michael is a 3-year-old boy referred by his preschool for assessment as he has clear cross-gender identification and behaviours. Michael's family is from Thailand and they have been resident in Australia for 12 months. The parents are non-English-speaking Buddhists and describe a belief system ascribing positive value to gender transition and an acceptance that some children are born as a 'third gender'. Michael's parents are aware that he is being teased at preschool and is having difficulties with his peers. There are adult trans-sexuals in the extended family. Michael is not discouraged from cross-gendered behaviour and the school has found it difficult to discuss issues with Michael's parents.*

Several issues and dilemmas are raised in this situation. Should Michael's family be encouraged to view Michael's development as disturbed and his cross-gender identification as pathological, even though they currently do not see it as such? Should the school environment be one that discourages Michael from expressing his cross-gendered interests even though he can express these at home? Is it possible to 'change' Michael's family's understanding of gender identity and is it ethical to attempt to do this? In practice, a key issue is working with Michael's stated difficulties with his peers and academic performance. Regardless of his family's acceptance of him, Michael is attempting to adapt to a peer group and community in which his experience is unusual and his position as cross-gendered may have negative effects on his ongoing development.

> Example 2: Sam
> *Sam is a 4-year-old boy from an Arabic family who presents with concerns that he is effeminate and 'homosexual'. Sam has some cross-gender interests but does not meet diagnostic criteria for GID. The family culture is one of significant homophobia and rigid models of gender-role behaviour. Sam's father is seeking genetic and hormonal investigation of Sam believing that he has a biological disorder. He has been physically punishing Sam for his behaviour.*

In this situation Sam is exhibiting gender-aberrant behaviour as defined by his family's cultural understanding of appropriate male behaviour. The immediate clinical concern is the degree of hostility directed towards Sam and the difficulty of engaging Sam's father. It may be necessary to involve culturally representative clinicians (if available) and to encourage involvement of all family members in initial negotiations in relation to an intervention framework. It is important to acknowledge and respect the family's concerns about Sam's development, and to contain immediate anxiety by offering appropriate support and to be cautious in 'challenging' the family's understanding of Sam's 'disorder' as biological in origin.

As these examples illustrate, cultural context influences both the presentation and understanding of gender dysphoria and gender-aberrant behaviour. Non-normative gender-role behaviour may in one context be seen as unproblematic variation (Example 1), while in another it may be defined as a disorder (Example 2). Different cultures will formulate any concept of 'gender disorder' according to varying models of sex-gender and the development of gender identity. They will also vary in concepts of the fixity or fluidity of gender identity and degrees of accommodation of gender transition. In some contexts it will be possible to adopt alternative or additional gender positions.

4.6.2 Child Assessment

Assessment of a child with gender issues needs to distinguish between cross-gendered behaviours (toy, play preference and peer activities) and identification (identity statements, role and fantasy play) and establish the degree of dysphoria or distress. Not all children express aversion towards their own bodies or a clear desire to change their body, and some children will be reluctant to disclose these feelings.

Comprehensive assessment involves exploration of parents' understanding and functioning, child's gender identity and overall child development. Several instruments are available including the Gender Identity Interview (Zucker 1995) and the Gender Male Questionnaire (Igntema and Cohen-Lettens, unpublished). For young children instruments focus on the ability to identify male and female and understanding of the stability of gender. The Draw-a-Person test provides important qualitative information regarding the child's gender concepts (Rekers et al. 1990).

4.7 Intervention Issues

Treatment approaches for children with gender dysphoria or GID vary according to the theoretical understanding of the condition and findings on assessment. Coates (2006), for example, states that there are likely to be multiple pathways to childhood GID and that not all have been adequately described in the literature. Treatment needs to be adapted to the needs of the particular child and family.

Approaches to intervention range from behavioural strategies aiming to reduce the expression of cross-gendered behaviour, to psychoanalytic approaches which seek to explore the psychological function and meaning of cross-gender identification. Broader psychosocial interventions include family psychoeducation and support and school-based interventions. There is ongoing debate about the purpose of treatment (and what is being treated), but also a recognition of 'gender difference' as having major developmental impact and of the importance of early intervention.

Behavioural approaches in the 1970s and 1980s (see Rekers 1995) saw GID as a result of inappropriate learning experiences and aimed to reinforce gender behaviours and skills. Cross-gender behaviours are discouraged and the family is trained in the application of reinforcement of gender-typical behaviour such as appropriate walking and athletic skills in boys. The relationship with the same-sex parent is encouraged to provide a role model. There are clearly several questions raised by this type of approach – the ethics of attempting to behaviourally control psychological identification; the potential for negative impact on self-esteem; and the rather narrow focus on external behaviour which does not look at broader developmental issues.

More recent approaches combine behavioural strategies with a psychodynamic understanding and work with the family to support the child's overall development. Meyer-Bahlburg (1985) describes working with parents to support the father-son relationship, promote gender-neutral interests and activities and support the child's peer relationships. Di Ceglie and Freedman (1998) focus less on changing the child's gender identity than on addressing developmental issues and family functioning. This way, for example, includes addressing separation anxiety, insecure attachment and depressive symptoms commonly found in boys with GID (Coates and Person 1985; Zucker 1995).

4.8 Puberty-Blocking Hormones

The use of puberty blockers (GnRH analogues) allows reversible suppression of 'puberty hormones' and the associated psychical pubertal changes. The rationale for their use is largely psychological, based on observations of the distress and depression that may accompany body change in transgendered adolescents. Suppression of puberty can reduce immediate anxiety and distress and supports ongoing psychological intervention and counselling.

The US Endocrine Society Guidelines from 2008 recommend use of GnRH analogues no later than Tanner stages 2–3 to suppress puberty in adolescents with a clear diagnosis of GID and introduction of cross-gender hormone treatment at age 16 years.

Geddes (2008) points out that some children will not continue to have transgendered feelings or cross-gender identification into adulthood although the proportion that revert to their original sex is unclear. Few trials have explored the long-term effects of delaying puberty in the age group and there are also concerns about the capacity to make informed decisions about this issue at the age of 12 or 15 years of age.

Debate is ongoing about the most appropriate treatment strategy for GID, particularly about the use of early hormonal treatment. The guidelines of the British Royal College of Psychiatrists (1998) support the use of (reversible) sex-steroid inhibitors where indicated with the aim of reducing distress and psychiatric workability. Others have cautioned again the use of puberty blockers on the grounds that these treatments will impact on emerging sexual identity which may be involved in a significant number of adolescents struggling with ego-dystonic homosexuality (Korte et al. 2008). It is also relevant that the course of GID in children is variable and plastic and that progression to trans-sexual development cannot be easily predicted in individual cases.

For younger children, work with families may support parents and provide important strategies for helping the child with gender variance manage ongoing developmental challenges and the broader social environment. Group approaches to parental support may be effective in reducing perceived isolation. Di Ceglie and Freedman (1998) note the importance of treating the cycle of secrecy around gender questions and enabling the child and family to tolerate uncertainty in gender-identity development.

Clinical management of children with gender issues often involves integrated psychological, social and biological interventions. In the current state of knowledge physical interventions are used cautiously and following comprehensive assessment. Providing parents and families with a clear planned and staged model of treatment is important and may help them deal with and ameliorate the child's distress.

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Abnormal Embryology in DSD

5

John M. Hutson

5.1 Failed Sex Determination

The first step in sexual differentiation is the activation of the *SRY* gene to trigger testicular development at 7–8 weeks of development. When there is a mutation or deletion of *SRY*, or one of the early downstream genes in gonadal differentiation, then the gonads fail to mature into either ovary or testis and become non-functional streak gonads. Failure of testicular development leads to absent male hormones required for masculinisation of both internal and external genitalia. This leads to regression of the mesonephric (Wolffian) duct and preservation of the paramesonephric (Müllerian) duct. The external genitalia continue on the female developmental pathway, leading to a normal external female phenotype at birth. The vagina and uterus form normally in the absence of MIS/AMH, while absent INSL3 leads to no swelling reaction in the gubernaculum, so the streak gonads occupy the normal position of ovaries.

A similar developmental pathway occurs in females with non-disjunction of the sex chromosomes leading to the 45,X genotype (Turner syndrome). In this circumstance, the primitive germ cells migrate from the caudal yolk-sac into the ambisexual gonad normally, but absence of the second X chromosome leads to abnormal development of the follicles, which undergo premature senescence in early childhood. The germ cells undergo premature death sometime between late foetal life and the first few years after birth. Biopsy of the gonad at birth or shortly after may show some primary follicles, but they regress within a few years, leaving the non-functional streak ovary that is the hallmark of Turner Syndrome (Fig. 5.1). Occasionally ovarian function persists until later in life in those patients with 45,X/46,XX mosaicism. Many foetuses (98–99%) with Turner syndrome fail to develop normally, leading to loss of the pregnancy.

In some rare forms of abnormal sex determination, there is complete sex reversal, with XY females or XX males. In the latter case, the common cause is translocation of a small segment of the Y chromosome, which includes the *SRY* gene, onto the X chromosome, usually at Yp11.3 (Table 5.1). This is now recognised by fluorescent in situ hybridisation (FISH) with a marker for the SRY gene.

5.2 46,XY Complete Gonadal Dysgenesis (Swyer Syndrome)

In this disorder there is an abnormality of the Y chromosome affecting the region of the *SRY* gene. In fact, in 15–30% of patients a mutation in this region can be identified (see Chap. 20).

Because SRY signalling is disrupted, the ambisexual gonads fail to differentiate into testes, and remain as non-functional streak gonads. Absence of male hormones allows normal female external development, and internally there is persistence of the Müllerian ducts into an infantile female genital tract. Additionally, the lower vagina still forms in the absence of androgens.

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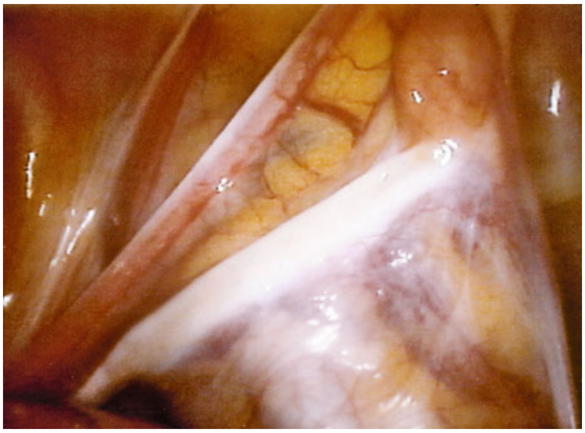


Fig. 5.1 Photo of a streak gonad taken at laparoscopy

The patients present at puberty with primary amenorrhoea and/or delayed development of secondary sex characteristics. Their stature is normal or tall, rather than short, as seen in Turner syndrome.

There is a high risk of development of a gonadal tumour by late adolescence, and in one series of 8 patients presenting between 13 and 18 years of age, 6 had tumours (gonadoblastoma and/or dysgerminoma) at the time of diagnosis (Zielinska et al. 2007).

Table 5.1 Sex reversal syndromes

Syndrome	OMIM no.	Genetics	Clinical features
Autosomal sex reversal syndrome	154230	DMRT1 gene deleted on 9p24	Females with 46,XY and pure gonadal dysgenesis
Campomelic dysplasia	114290	SOX9 haplo-insufficiency at 17q24.3–q25.1	Females with 46,XY gonadal dysgenesis bowed long bones
Dosage-sensitive sex reversal	300018	DAX1 duplication at Xp21.2–21.3	Females with 46,XY gonadal dysgenesis
Rutledge lethal multiple anomaly syndrome	268670	7-dehydrocholesterol reductase gene mutation at 11q12–13	Females with 46,XY polydactyly Congenital heart defects Renal + pulmonary hypoplasia
46,XY complete gonadal dysgenesis (Swyer syndrome)	306100	SRY mutation/deletion at Xp21.2–22	Females with 46,XY gonadal dysgenesis
XX male syndrome	278850	SRY translocation to X chromosome (Yp11.3)	Males with 46,XX

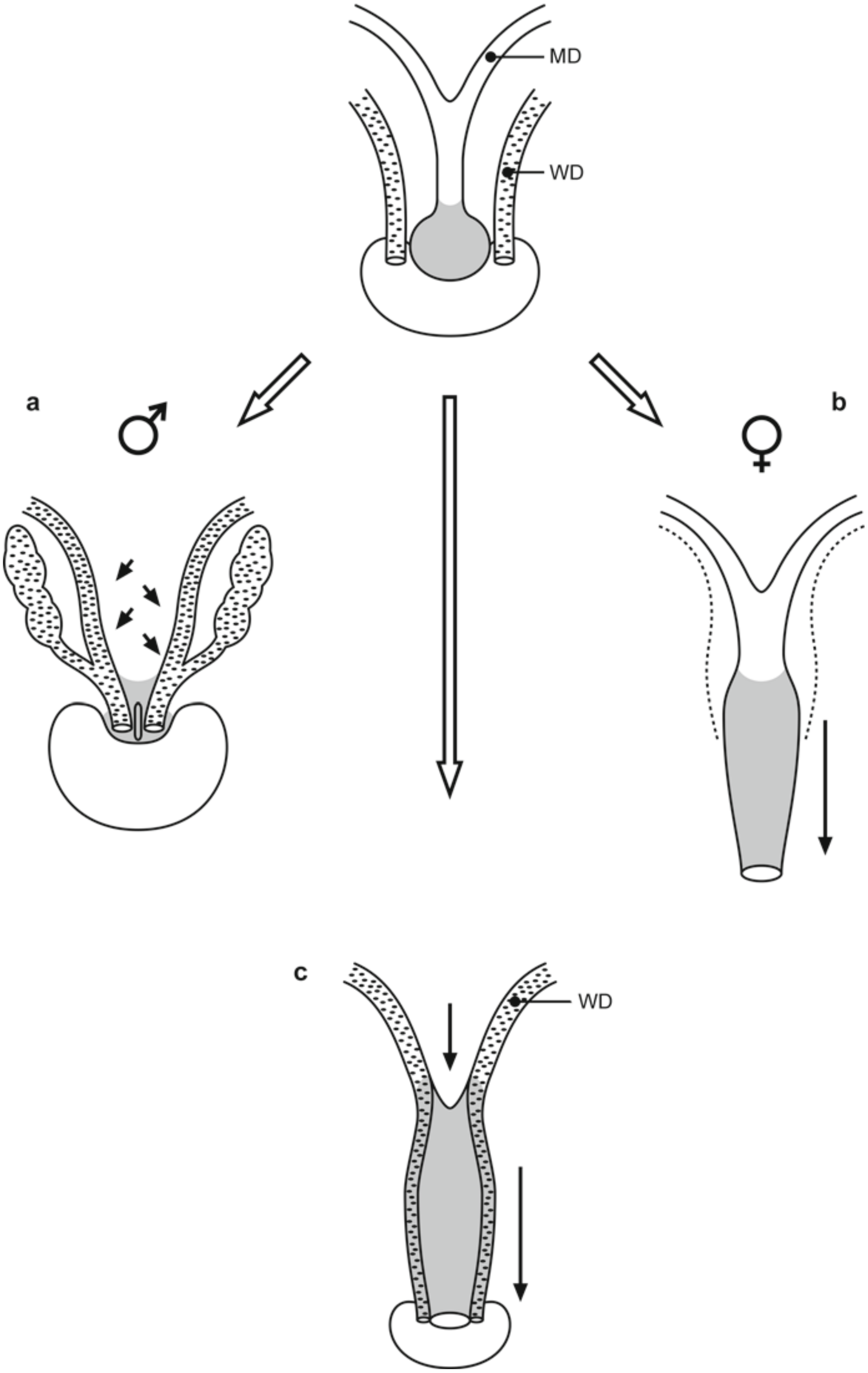
5.3 Failure of Testicular Differentiation

The genetic pathway regulating testicular development after SRY activation remains almost completely unknown. Although the downstream genes themselves remain obscure, it is possible to predict that mutations in these genes may produce various forms of gonadal dysgenesis. This may include decrease in overall testicular size (testicular hypoplasia), so that the total volume of hormone production is significantly decreased. This will lead to impaired virilisation of both the internal and external genitalia (Fig. 5.2). Also, delayed onset of testicular differentiation may produce a testis with apparently normal function postnatally, but the delay will result in impaired sexual differentiation which occurs between 8 and 12 weeks of development.

A more common cause of testicular mal-development occurs in mixed gonadal dysgenesis (45,X/46,XY) related to mosaicism of the sex chromosomes. This may produce two dysplastic testes, but more commonly, the mosaicism is segregated so that one gonad develops into a testis (with or without variable dysplasia) while the other gonad becomes a non-functional streak. This form of DSD produces variable degree of virilisation on each side, as the male hormones are only present on one side, leading to preservation of part or all of the Wolffian duct on the testicular side, while the Müllerian duct is preserved on the side of the streak gonad (Fig. 5.3) (Ben-Meir and Hutson 2005).

Although asymmetry is not obvious in the normal genital tract, in the rest of the embryo there is marked asymmetry, with the primitive heart tube looping to the right side and the abdomen showing major anatomical differences in the organs on each side (Goldstein et al. 1998). The sidedness of the embryo is programmed into the development when the embryonic disc is developing the primitive streak, which is responsible for co-ordinating the three-dimensional axes of the future embryo, cranio-caudal, dorso-ventral, and left-right. Quite a lot is now known about the genes controlling left-versus-right sidedness, with the initial

Fig. 5.2 (**a**) Müllerian duct (*MD*) regressed with normal MIS levels in a male. (**b**) Normal downgrowth of vaginal plate to vestibule and regression of Wolffian ducts in a female. (**c**) Wolffian ducts (*WD*) incorporated into side of vaginal plate secondary to moderate testosterone levels in 5α reductase deficiency. Partially inhibited downward growth of conjoined urogenital sinus opening secondary to inadequate DHT levels (Reproduced with permission from Ben-Meir and Hutson 2005)



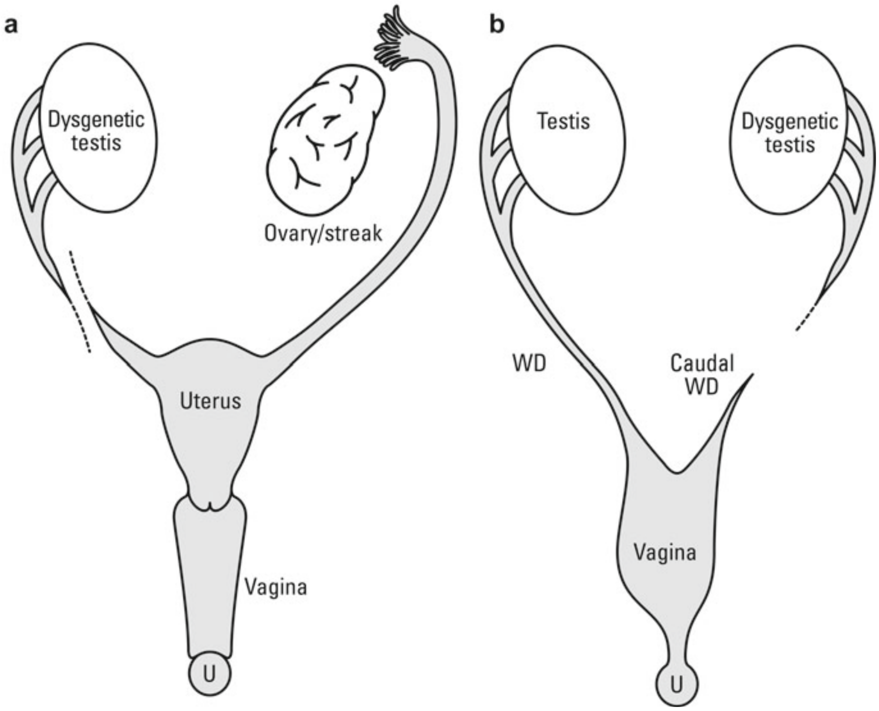


Fig. 5.3 (**a**) Variant of gonadal dysgenesis (as in MGD or Ovotesticular DSD): unilateral, poorly developed testis leads to local epididymal preservation only, with persistence of contralateral as well as distal ipsilateral Müllerian duct, secondary to inadequate exocrine function. Vagina is also preserved because of inadequate endocrine function. (**b**) Variant of gonadal dysgenesis (*MGD*): unilateral well-developed testis leads to complete ipsilateral Wolffian duct as well as caudal end of contralateral duct. Contralateral poor gonad only produces enough androgen to preserve the epididymis. Inadequate endocrine function leads to partial vaginal development. *U* urethra, *WD* Wolffian duct (Reproduced with permission from Ben-Meir and Hutson 2005)

signal for left versus right being determined by the cilia on the surface of cells at the base of Hensen's node (Nonaka et al. 1998; Takeda et al. 1999; Marszalek et al. 1999; Vogan and Tabin 1999). Genes encoding for molecular motors, called kinesins, are responsible for allowing these very special mono-cilia in Hensen's node to rotate clockwise, like propellers (Supp et al. 2000). The rotating mono-cilia create a micro-current in the shallow pit of Hensen's node which forces any signalling molecules produced by the cells to be pumped to the left side, which normally triggers activation of sonic hedgehog (SHH) gene on the left side. This initiates different development on the left side of the embryo from the right, which shows up as the asymmetry of the cardiovascular and gastrointestinal systems (Rodriguez Esteban et al. 1999).

Abnormalities of the molecules regulating mono-cilial movement in Hensen's node cause situs inversus in both humans and animal models. Kartagener syndrome, with situs inversus, chronic sinusitis and recurrent pneumonia causing bronchiectasis, is caused by a defect in cilial functions (Afzelius 1976, 1999). There are knockout mice with defective KIF3A/B, iv and inv genes that also show situs inversus (Handel and Kennedy 1984; Yokoyama et al. 1993; Brueckner et al. 1991) (Box 5.1).

Box 5.1 Asymmetry of the Urogenital Ridges in Normal Birds and Humans with DSD

The overriding asymmetry of the body of vertebrates is mostly concealed in the urogenital tract, although it is not only obvious, but also completely normal in birds (Hutson et al. 1983). In the chick embryo the urogenital ridges are symmetrical in males, but in the female embryo there is distinctive asymmetry. Initial ambisexual stages of development are symmetrical, but once the gonads begin to develop the left gonad forms a normal ovary, but the right gonadal development is partly testicular, forming an ovo-testis. Indeed, the right gonad produces sufficient MIS/AMH to cause regression of the right Müllerian duct, so that the female ends up with a uterus forming from only the left Müllerian duct (Hutson et al. 1983). Although the MIS/AMH circulates through the blood, the left Müllerian duct is relatively resistant to regression, related to different expression of oestrogen receptors, which protect it from regression. The right ovo-testis is vestigial in a young hen, but may degenerate later in life with development of gonadal tumours with full-blown development of testicular hormones, which may masculinise the aging hen (Hutson et al. 1983).

The asymmetrical urogential ridge in birds shows that the two sides can differentiate differently, with the right side being more 'masculine'. It is fascinating to observe similar sidedness in humans with asymmetrical gonadal development, where, as in birds, the right side of the body is more likely to be the masculine side. In babies with mixed gonadal dysgenesis and ovo-testicular DSD it is the right gonad which is more likely to be testis, while the left gonad is more frequently an ovo-testis, streak gonad or ovary (Forest 2006).

5.4 Anatomy of Caudal Internal Ducts in DSD

The Wolffian duct persists as epididymis and vas deferens in most patients with 45,X/46,XY MGD ipsilateral to a dysgenetic testis (Zah et al. 1975). In a series of 15 patients with MGD, Alvarez-Nava and co-authors found only 1 child with Wolffian duct structures on the same side as the streak gonad (Alvarez-Nava et al. 1999). In another series of 14 patients with MGD, 7 had a vas deferens on the same side as the dysgenetic testis (Donahoe et al. 1979). At the caudal end of the internal ducts, the vas deferens has been reported to enter into a persisting Müllerian duct or vaginal remnant (Ben-Meir and Hutson 2005). This has also been reported in ovo-testicular DSD (Nihoul-Fekete et al. 1984).

The association of internal genital ducts with ipsilateral gonadal development was likely to be caused by the males hormones (testosterone and MIS/AMH) being secreted down the Wolffian duct in an exocrine fashion (Tong et al. 1996). In an in vitro study of the urogenital ridge fluorescent androgen injected into the testis did not diffuse radially from the site of injection within the testis, but was immediately transported into and along the Wolffian duct, so that within a few hours of culture nearly all the fluorescence was found within the distal Wolffian duct, consistent with active transport along the duct system. This exocrine secretion of hormones into the Wolffian duct is not surprising, when one appreciates that it was functioning just before sexual development as the excretory duct of the 'middle kidney', or mesonephros, and that some small amounts of 'urine' pass down the duct to the cloaca.

The anatomy of the caudal ends of the Wolffian and Müllerian ducts is predictable when it is assumed that testosterone and MIS/AMH pass down the Wolffian duct from the ipsilateral gonad. When a dysgenetic testis is produced, the amount of ipsilateral Wolffian duct that persists will be directly proportional to the amount of testosterone that is manufactured. If the testis is well formed, the entire Wolffian duct will be preserved. By contrast, however, when the gonad forms a dysplastic testis, only the most proximal part of the Wolffian duct will persist to form epididymis and some proximal vas deferens. Regression of the Müllerian duct is the mirror image of this, so that where only the proximal Wolffian duct is preserved, the distal Müllerian duct may persist as a blind-ending fallopian tube or uterine horn. By contrast, inhibition of development of the vaginal plate to form the vagina requires circulating androgens and conversion of testosterone to DHT. This can lead to unusual variants where the Wolffian duct has been preserved by exocrine action of androgen secreted down the duct, but there is inadequate endocrine function of androgens so that there is a vaginal remnant and deficient seminal vesicles (Fig. 5.3).

5.5 Placental Failure

In the developing embryo the initial production of testicular hormones was thought to be autonomous, as the foetal hypothalamus and pituitary are not functional until around 15 weeks of development (Forest 2006). Recent evidence, however, suggests that the early testis is probably responding to stimulation by the placenta, which produces chorionic gonadotrophin (hCG). This trophic effect of placental hormones may be more important than once thought, as demonstrated in some babies with severe intra-uterine growth retardation (IUGR) and extreme prematurity. We have seen a number of extremely premature male infants with severe IUGR with undervirilisation of the external genitalia, suggesting insufficient androgen production between 8 and 12 weeks, secondary to placental failure. By the time the foetal hypothalamic-pituitary axis is functional the genital ambiguity is permanent. Subsequent investigations postnatally have revealed no endocrinopathy, although the placentas were reported to be very hypoplastic.

5.6 Failure of the Hypothalamic-Pituitary-Gonadal Axis

The foetal nervous system develops at a different rate from the urogenital tract, and abnormalities of hypothalamic or pituitary function have a characteristic appearance in males. As mentioned above, the pituitary begins producing trophic hormones (FSH, LH) to regulate testicular function at about 15 weeks of development. Where there is a structural anomaly (e.g. septo-optic dysplasia) or a molecular defect in hormone-signalling pathways (LH mutation, LH receptor mutations), the internal and external genitalia will have masculinised normally in a male by 15 weeks. However, development thereafter will be inhibited by lack of testicular hormone secretion, leading to cessation of phallic growth. Male babies with hypothalamic or pituitary disorders have normally formed external genitalia (indicating normal hormone levels between 8 and 12 weeks), but inadequate subsequent penile growth, leading to micropenis. In addition, because testicular descent occurs later in development, and this second step requires androgens, the inguino-scrotal phase of testicular descent is likely to be disrupted, leaving undescended testes palpable in the inguinal regions (Fig. 5.4).

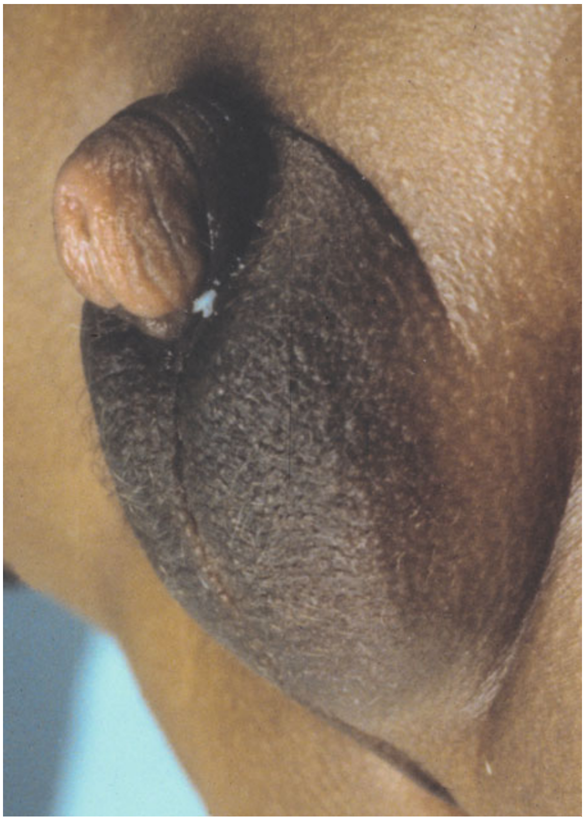


Fig. 5.4 External genitalia of a boy with micropenis, secondary to inadequate androgenic stimulation in the second half of pregnancy, when the foetal hypothalamic-pituitary-gonadal axis should be functioning

5.7 Failure of Hormone Action

5.7.1 INSL3

INSL3 is produced by the Leydig cells and is known to cause the swelling reaction in the gubernaculum, enabling its distal end to enlarge in males, thereby preventing its elongation with foetal growth, as occurs in the female, where the gubernaculum elongates into the round ligament and ligament of the ovary. The swelling reaction occurs about 10–15 weeks of development in the human. Failure of INSL3 production, or mutations in its gene or receptor (LGR8), would produce failure of the transabdominal phase of testicular descent. A number of authors have screened boys with cryptorchidism for anomalies in the INSL3 or LGR8 genes, but to date only a small number of cases have been reported (Adham and Agoulnik 2004).

5.7.2 MIS/AMH

The Sertoli cells produce MIS/AMH, which diffuses down the Wolffian duct to reach the adjacent ipsilateral Müllerian duct. Mutations in the MIS/AMH gene or its receptor produce a unique genital anomaly known as the persistent Müllerian duct syndrome (PMDS) (Hutson et al. 1987, 1994; Hutson and Baker 1994). In this rare anomaly the Müllerian ducts persist as an infantile female genital tract in an otherwise normal male, whose only other anomaly is cryptorchidism. Although INSL3

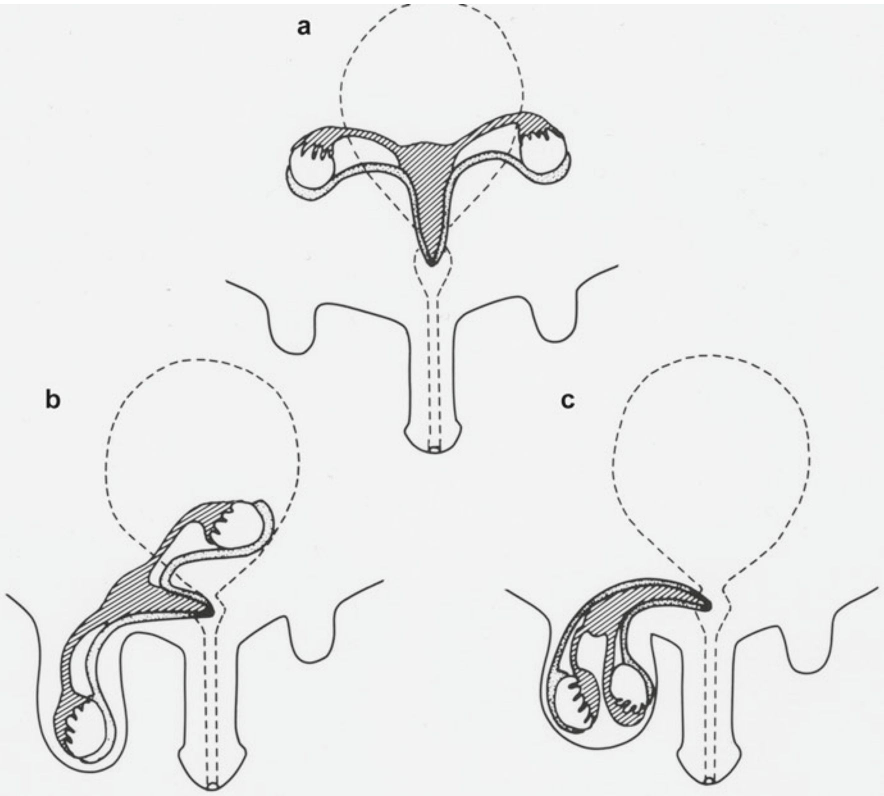


Fig. 5.5 The three clinical presentations of the persistent Müllerian duct syndrome. The testis is highly mobile due to regression of the cranial suspensory ligament and the presence of a long and thin gubernaculum. (**a**) Most (60–70%) patients have testes in the normal position of ovaries and the inguinal sacs remain empty. (**b**) A smaller group (20–30%) have one testis in an inguinal hernia along with its attached tube and uterus. This is known as 'hernia uteri inguinalis'. (**c**) About 10% of patients have both testes herniated into one processus vaginalis (transverse testicular ectopia) (Reproduced with permission from Hutson et al. 1987)

is known to be the primary hormone regulating the swelling reaction in rodents, MIS/AMH has been shown to have a subsidiary role in gubernacular enlargement in organ culture and the gubernaculum contains MIS/AMH receptors (Kubota et al. 2002; Fu et al. 2004).

It is quite likely that the role of MIS/AMH on gubernacular development is more significant in humans than in rodents, as in boys there is a very tight link between Müllerian duct regression and ipsilateral descent of the testis (Scott 1987; Abe and Hutson 1994).

In boys with PMDS, there are three main clinical presentations, depending on the location of the testes (Fig. 5.5). Because androgenic function is normal the cranial suspensory ligament has regressed, and despite the persistence of the Müllerian ducts, the broad ligament is hypoplastic (perhaps because of the absence of oestrogens). Abnormality of the swelling reaction, with failure of the gubernacular cord to remain short, leads to the gubernaculum being abnormally long, even longer than a normal round ligament in a girl. As androgen production and action is unimpeded, the second phase of testicular descent, migration of the caudal end of the gubernaculum to the scrotum appears to be relatively normal, despite abnormality of the transabdominal phase of descent. This leaves the inguinal canals open with a patent processus vaginalis extending into the hemiscrotum. The testis, however, rather than being within the scrotum and attached by a short gubernacular cord to the inside of the processus vaginalis, is usually located within the abdomen attached to a greatly elongated gubernacular cord (Fig. 5.6).

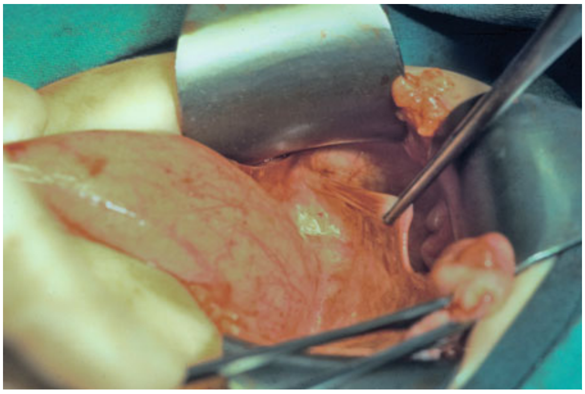


Fig. 5.6 Intra-operative photograph of a boy with PMDS showing the elongated gubernacular cord more than 10 cm long extending from the right internal inguinal ring to the right testis out of focus in the foreground

In the commonest clinical variant described in the literature, both testes are in an 'ovarian' position within the abdomen and the inguinal hernial sacs remain empty

(60–70%). There is a smaller group, comprising 20–30% of all cases described, where one testis is located within an inguinal hernia, along with its attached fallopian tube and infantile uterus. This variety is known as 'hernia uteri inguinalis'. In the remaining 10% of patients both testes are found within the same patent processus vaginalis, producing transverse testicular ectopia. At operation the testes are not anchored to the inside of the processus vaginalis in the normal way, as the gubernaculum is so long it can permit herniation of one testis out into a contralateral hernial sac! In one of these cases witnessed by the author, delivery of the contents of a right inguinal hernia in a phenotypic boy with a left cryptorchid testis (palpable in the groin) led to the left testis disappearing into the abdominal cavity and reappearing in the right inguinal hernia! These findings suggest that 'descent' of the testis into the groin or scrotum in PMDS is actually prolapse of a highly mobile genital tract, rather than normal testicular migration.

Many authors have come to a contrary explanation for cryptorchidism in PMDS, concluding that testicular descent was passively impeded by the attachments of the broad ligaments and fallopian tubes (Josso et al. 1993). The highly mobile genital tract in PMDS is such that the entire internal genital tract can be delivered out of a laparotomy wound for photography, in a way which is not possible in either normal males or females (Fig. 5.7). By contrast, if the cause of cryptorchidism was merely passive prevention of gonadal descent by the persistent Müllerian ducts, one would expect the testes to be closely bound to each internal inguinal ring by a normal gubernacular cord. Clearly, this is not the case in PMDS.

The most useful deduction from knowledge of PMDS is the tight link between Müllerian duct regression and testicular descent in babies with DSD. Where the testis is palpable in the groin in a baby with ambiguous genitalia, we can predict that the ipsilateral Müllerian duct has undergone regression, and hence there will be no fallopian tube and uterine horn on that side.

5.7.3 Androgen

Failure of androgen production is most commonly caused by a mutation in the enzyme 17β-hydroxysteroid dehydrogenase-3 (17β-HSD3). Androgen production is frequently suppressed so severely that the external genitalia are completely or nearly completely female at birth. The first clue to the disorder may be signs of virilisation and primary amenorrhoea at puberty. Despite 46,XY chromosomes and undescended testes in the inguinal canals or groins, these patients usually have a female gender orientation, suggesting that significant androgens are necessary during foetal development or in the postnatal 'minipuberty' for gender development (Hrabovszky and Hutson 2002). Minor virilisation at puberty is probably related to excessive hypothalamic drive (because negative feedback is deficient), which causes testicular enlargement and allows testosterone production to increase even when the mutation has deactivated the enzyme by 95%.

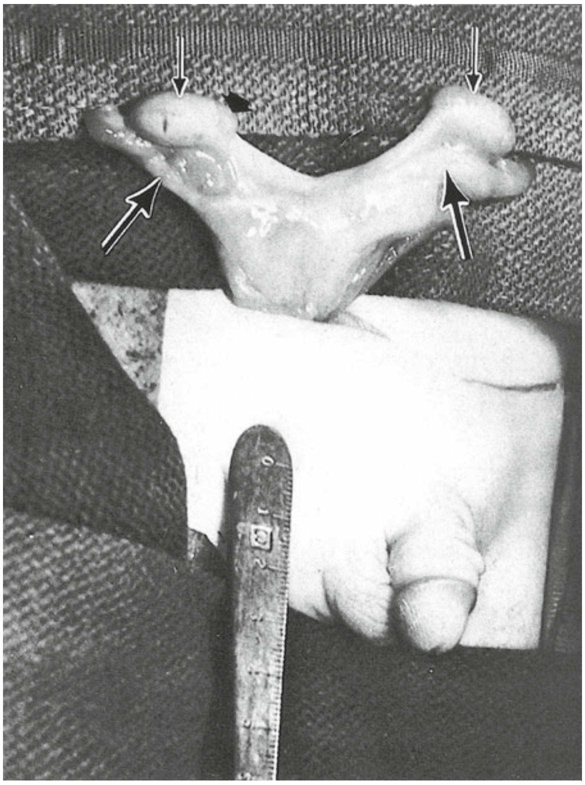


Fig. 5.7 Photograph of the genital tract being delivered from the wound during a laparotomy for a boy with PMDS (Miller et al. 2004, reproduced with permission of the publisher)

Mutations of the androgen receptor gene lead to complete or partial androgen insensitivity syndrome (CAIS or PAIS), depending on the remaining function of the receptor. The external genitalia are completely feminine in CAIS, confirming that androgens are essential for masculinisation. As the testis has normal Sertoli and Leydig cell function, MIS/AMH production is normal and the Müllerian ducts regress. Absence of negative feedback leads to testicular hypertrophy

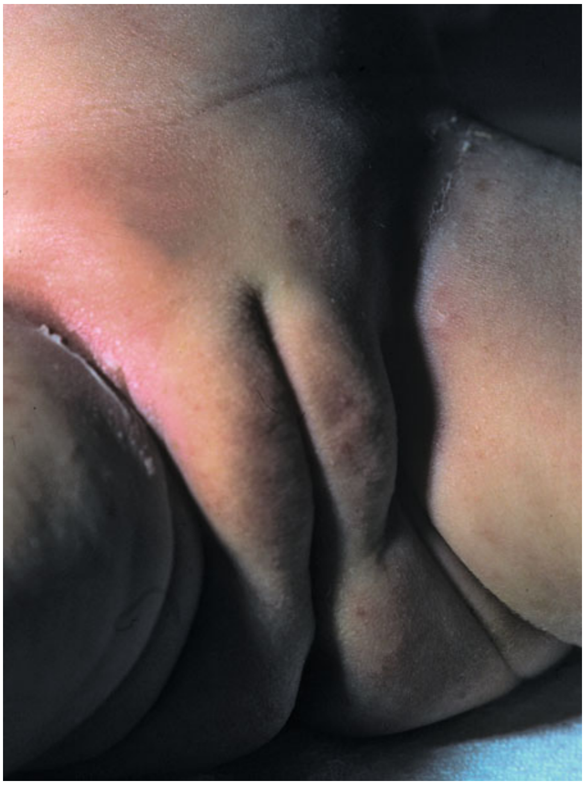


Fig. 5.8 A 1-week old girl (46,XY) with complete androgen resistance and normal female phenotype. The trans-abdominal migration of the testes is normal, but inguino-scrotal migration is absent, leaving the testes in the groin (Clarnette et al. 1997, reproduced with permission)

from pituitary stimulation. The testes are in the inguinal canals or groins, as the first phase of testicular descent is normal (Fig. 5.8). Gender orientation is female in CAIS, and either male or female in PAIS, depending on the level of androgen receptor function and the amount of exposure, although the exact predictors for brain sex remain to be determined (Hrabovszky and Hutson 2002).

α-Aromatase mutations lead to virilisation of both foetus and mother, as not only the foetus but also the placenta is unable to neutralise any foetal androgens by conversion to oestrogens in females.

Mixed effects on the male fetus are seen where there is a 5α-reductase-2 gene mutation, leaving the external genitalia under-virilised. Masculinisation of the brain, however, seems less affected, as patients are reported to develop normal male gender identify at puberty, when testicular growth occurs. This suggests that 5α-reductase-2 is less important in the brain than the genitalia, perhaps because sexual dimorphism of the brain is occurring later in gestation when circulating androgen levels may be higher than at 8–12 weeks when the testis first develops.

5.8 Anormal Morphogenesis of the Genitalia (See Also Chap. 9)

Failure of ingrowth of mesenchyme from the peri-umbilical region and from the primitive streak to migrate around the cloacal membrane may prevent normal development of the lower anterior abdominal wall and genital tubercle, which may lead to bladder exstrophy. Recent evidence suggests that genes involving differentiation of abdominal wall muscle and the anterior bladder muscle may be involved (Lund and Hendren 2001; Reiner and Gearhart 2004; Ngan and Mitchell 1997; Cheng et al. 2006), and P63 has been identified as a possible candidate, as knockout mice develop bladder exstrophy (Lund and Hendren 2001; Reiner and Gearhart 2004; Ngan and Mitchell 1997; Cheng et al. 2006).

The genitalia are abnormal because of failure of fusion of the pubic bones and exposure of the bladder and urethral mucosa as a flat plate. In females the glans of the clitoris is in two separate halves and the vagina is oriented almost directly forwards, rather than downwards. In males the urethral plate is on the dorsal surface of the corpora cavernosa, which are short and curved upwards, producing reversed chordee. In both sexes the anterior abdominal wall is deficient, with not only exposure of the bladder mucosa, but also foreshortening of the normal distance between the umbilicus and the perineum (Fig. 5.9a).

An even more severe anomaly of the urogenital tract may occur that includes failure of separation of the hindgut from the urogenital sinus in the primitive cloaca. This leads to the rare defect of cloacal exstrophy, where the external genitalia are disrupted by the presence of not only the open bladder plate (in 2 halves) laterally, but also the dysplastic hindgut and midgut, represented by the open caecum (Fig. 5.9b). The internal genital tracts are widely separate, and often obstructed, leading to haematometra and/or haematocolpos in adolescent girls. The cause of this extremely disabling anomaly remains unknown, but it

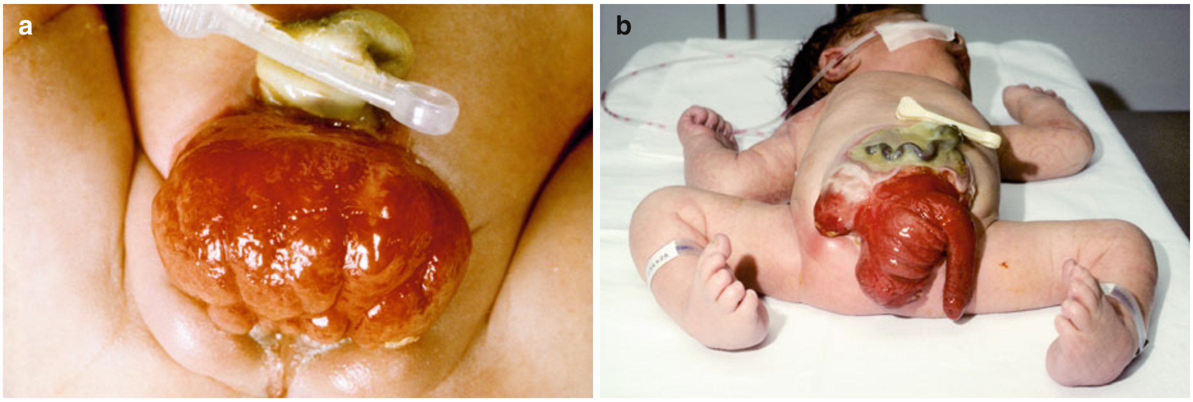


Fig. 5.9 (**a**) Genital abnormality secondary to bladder exstrophy, where the primary anomaly lies in failure of development of the mesoderm forming the anterior lower abdominal wall. (**b**) The rare defect of cloacal exstrophy, where not only is the anterior abdominal wall deficient, but also there is failure of subdivision of the primitive cloaca into urogential tract anteriorly and hindgut posteriorly

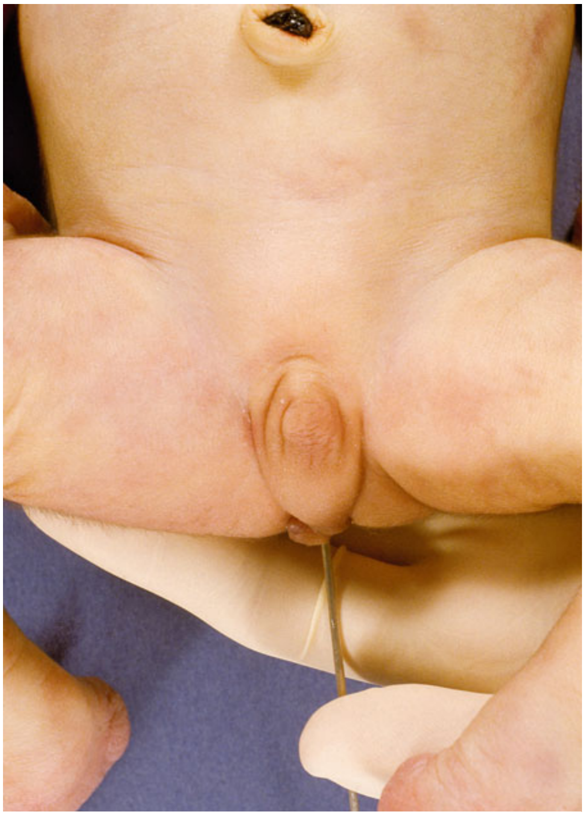


Fig. 5.10 Agenesis of the phallus in a baby with an empty scrotum with no midline septum (Srinivasan et al. (2003) reproduced with permission of the publisher). (Probe in perineal fistula as anus is absent)

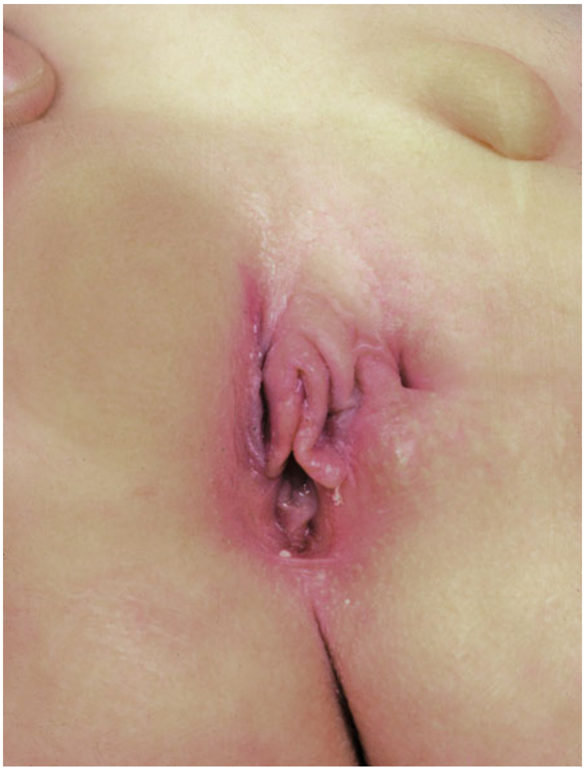


Fig. 5.11 Ectopic labium

is recognised to be associated with numerous other malformations, including neural tube defects and hindgut anomalies.

Formation of the genital tubercle may be deranged in the rare anomaly of penile agenesis. In this condition the genital tubercle is completely absent in an otherwise phenotypic male with testes descended into the scrotum (Fig. 5.10). When the median scrotal raphe is absent then there is a very high incidence of severe urinary tract anomalies, including absent kidneys (Srinivasan et al. 2003). The urethra is usually connected to the anterior rim of the anal canal, consistent with aberrant separation of the urinary and gastrointestinal tracts. Urine is seen to dribble from the anus through this ectopic urethra, which is similar in anatomy to an H-fistula in some rare variants of anorectal malformations (Holschneider and Hutson 2006). The ectopic urethra usually has some erectile tissue around it analogous to aberrant corpus spongiosium.

The genital folds may sometimes be aberrant and may fail to be present or be located ectopically. The latter anomaly leads to ectopic scrotum or labia (Fig. 5.11). When the hemiscrotum is ectopic, it is usual for the testis to descend into it, suggesting that its innervation by the genitofemoral nerve is intact, and the gubernaculum has migrated into the ectopic scrotum under correct chemotactic guidance by the genitofemoral nerve (as described in Chap. 2).

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46,XX Disorders of Sex Development

6

Garry L. Warne and Jacqueline K. Hewitt

6.1 Clinical Presentations of Patients with 46,XX DSD

An infant or child with one of the 46,XX disorders of sex development may present with:

- *Ambiguous genitalia*. More than half of all infants born with ambiguous genitalia are 46,XX. Their atypical genital appearance, which is due to varying degrees of phallic enlargement and labial fusion, results from in utero exposure to excess androgen. The source of the excess androgen may be adrenal (as in congenital adrenal hyperplasia) or testicular (46,XX being the most common karyotype associated with ovo-testicular DSD) (Krob et al. 1994) (see Chap. 8 for a full description). Sometimes the source of androgens is maternal ingestion or maternal androgen-secreting tumours.
- *A complex congenital malformation*, such as cloacal extrophy or bladder extrophy (these are described in Chap. 9).
- *Gradual enlargement of the clitoris during childhood, and other signs of virilisation*. This may be seen in girls with non-classic CAH (see Chap. 12).
- *Abnormal development at puberty* (see Table 6.1, Chap. 13). The girl may have primary amenorrhoea and either *no* breast and pubic hair development (46,XX gonadal dysgenesis, steroid biosynthetic defects); or
  - *Normal* breast and pubic hair development (Müllerian duct agenesis); or
  - *Normal breast development but little or no pubic hair* (complete androgen insensitivity syndrome)

6.2 Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a *family* of genetically determined conditions caused by deficiencies of steroidogenic enzymes in the adrenal cortex (Hughes 1990a). In some forms of CAH, such as lipoid CAH, ovarian steroidogenesis is also impaired (Table 6.2). In relation to each type of CAH, the terms classic and non-classic are used to distinguish grades of severity. In the classic form, prenatal development of the genitalia is affected, whereas in the non-classic form, the first effects on sex development occur after birth.

6.2.1 21-Hydroxylase Deficiency

The classic form of 21-hydroxylase deficiency is the single most common cause of ambiguous genitalia. It is potentially lethal, in that 75% of cases have the salt-wasting (SW) form and from the end of the first week of life, they are at risk of an adrenal crisis or death. Many countries have established newborn screening programs for CAH, aimed at preventing these deaths (White and Medscape 2009). Infants with salt-wasting CAH will inevitably die unless the correct diagnosis is made and appropriate treatment promptly started. The other 25% of cases have the simple virilising (SV)

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Table 6.1 46,XX conditions that present with abnormal development at puberty

Condition	Breast/pubic hair development	Menstruation	Distinguishing feature
46,XX gonadal dysgenesis	–	–	↑ FSH & LH, ↓ E2. FSH receptor gene mutation
17α hydroxylase deficiency	–	–	Hypertension, hypokalaemia. ↑mineralocorticoids, ↓ cortisol and sex steroids. Mutation in *CYP17*
Steroidogenic factor-1 deficiency	+/–	Primary amenorrhoea or premature ovarian failure	Mutation in *NR5A1*
Mullerian duct agenesis	+	–	Normal hormone levels, anatomical anomaly seen on imaging. *WNT4* mutations in some cases

Table 6.2 Summary of the different types of CAH causing 46,XX DSD

Type of CAH	OMIM #	Expressed in adrenal	Expressed in ovary	Virilisation	Hypertension	Salt wasting
21-hydroxylase deficiency	201910	+	–	+	–	+
11β-hydroxylase deficiency	202010	+	–	+	+	Transient neonatal (before treatment)
3β-HSD[a] deficiency	201810	+	+	+	–	+
P450 oxidoreductase deficiency	124015	+	+	+	–	+/–
17α-hydroxylase deficiency	202110	+	+	–	+	–
Lipoid adrenal hyperplasia	201710	+	+	–	–	+

[a] 3β-hydroxysteroid dehydrogenase

(or non-salt-wasting) form; they have milder adrenal insufficiency, are able to maintain normal electrolyte homeostasis and have a lower risk of adrenal crisis.

Deficiency of 21-hydroxylase impairs the conversion of 17-hydroxyprogesterone to 11-deoxycortisol in the zona fasciculata of the adrenal cortex, resulting in cortisol deficiency. This stimulates an increase in pituitary ACTH secretion, which increases the production of adrenal androgens (DHEA and androstenedione) and these are converted to testosterone and DHT, inducing masculinisation of the genitalia in a female foetus. The enzyme deficiency also impairs the conversion of progesterone to 11-deoxycorticosterone in the mineralocorticoid pathway, lowering aldosterone production. While only the SW form of CAH is associated with severe aldosterone deficiency and serum electrolyte imbalance, aldosterone production is also impaired in the SV form; in most cases, plasma renin activity and plasma angiotensin II are increased (Rosler et al. 1977), indicating salt depletion. Angiotensin II stimulates ACTH secretion, so when there is salt depletion and levels of angiotensin II are elevated, the pituitary is relatively resistant to the negative feedback from cortisol and higher glucocorticoid doses will be needed to treat the patient (Rosler et al. 1977).

6.2.1.1 Clinical Features

A typical 46,XX infant with classic 21-hydroxylase deficiency will have:

- Ambiguous genitalia, but no palpable gonads (Fig. 6.1)
- Hyperpigmentation of the genital skin, due to excess ACTH
- A uterus
- Evidence of a possible metabolic disturbance if steroid treatment has been delayed – hypoglycaemia, hyponatraemia, hyperkalaemia (classic SW form, after the first week)
- Absence of any dysmorphic features that might suggest aneuploidy

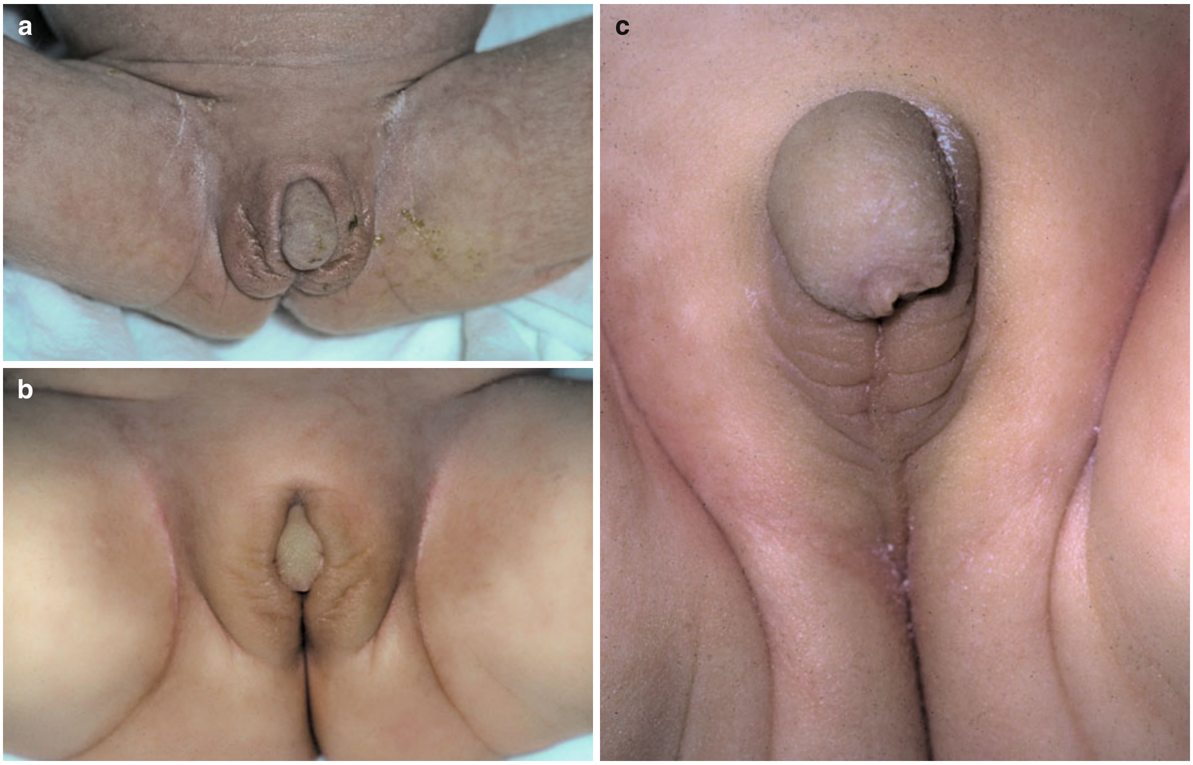

Fig.6.1 (**a**) External evidence of exposure to androgens in this 46,XX female with CAH and Prader3 virilisation at birth. Note pigmentation and wrinkling of fused labio-scrotal folds but no visible gonads. (**b**) The same baby at 8 weeks of age at the time of genital reconstruction, showing some regression of the virilisation after commencing steroid treatment. (**c**) Another baby girl with 46,XX DSD with CAH caused by a more severe defect in 21-hydroxylase leading to more severe virilisation (Prader 4–5)

6.2.1.2 Diagnosis

- Serum 17-hydroxyprogesterone (>700 nmol/L in classic form; 70–500 nmol/L in non-classic form; Levine et al. 1981).
- Urine steroid analysis by gas chromatography-mass spectrometry (Wudy et al. 2000). Characteristic peaks of pregnanetriol and pregnanetriolone confirm the diagnosis of 21-hydroxylase deficiency and differentiate it from other virilising forms of CAH, such as 11β-hydroxylase deficiency.
- Serum electrolytes – after the first week in an untreated infant with the SW form, serum sodium falls and potassium rises.
- Blood glucose – may be low due to cortisol deficiency.
- Imaging studies (see Chap. 14)
  - Pelvic ultrasound confirms presence of uterus
  - Urogenital sinugram defines length of the urogenital sinus and site of junction between urethra and vagina

6.2.1.3 Genetics

Deficiency of 21-hydroxylase is inherited as an autosomal recessive trait. The gene frequency in the general community is 1:55 (Baumgartner-Parzer et al. 2005). The gene which encodes this enzyme is cytochrome P450c21 (also known as CYP21A2; OMIM 201910), which is located on chromosome 6p21.3, contiguous with genes for complement and the major HLA loci (Levine et al. 1978). Close by is a pseudogene called CYP21A, which, compared to the CYP21A2 gene, is missing 8 basepairs from exon 2, making it inactive. The presence of the pseudogene complicates mutational analysis (Koppens et al. 2002). To date, more than 174 CYP21A2 deletions and point mutations have been reported (Finkielstain et al. 2011; Concolino et al. 2010). These may be exonic or intronic (in fact, the commonest mutation is an intron 2 frameshift mutation; Speiser and White 2003). Many of the point mutations are examples of gene conversion, i.e. the structure of the active gene has reverted to that of the pseudogene (Higashi et al. 1986). Structure-function correlations have been studied for the most common mutant alleles (Chung et al. 1995; Robins et al. 2006). In one large series, 79% of individuals with CAH were compound heterozygotes. Genotype accurately predicted phenotype in 90.5%, 85.1% and 97.8% of patients with salt-wasting, simple virilising, and non-classic mutations, respectively (Finkielstain et al. 2011).

Once a couple has had one child with CAH, they can be offered prenatal diagnosis in any subsequent pregnancy. The genotypes of the parents and the index case are used to identify the pathogenic mutation, and then CVS or amniotic fluid can be tested using PCR.

6.2.1.4 Patient Follow-up and Monitoring of Treatment

In children with CAH, growth velocity, weight gain, blood pressure, sexual development and general well-being are followed at 3–4 monthly intervals. The aim of treatment is to allow growth to follow the normal centiles without excessive weight gain, for blood pressure to be normal, and for general health to be good, without episodes of adrenal crisis. Parents need education in how to prevent adrenal crises and are given several rules to follow. These are: that they should never stop the child's steroid medications unless instructed to do so by a doctor; that intercurrent illnesses, especially those associated with fever, should be covered by trebling the child's usual glucocorticoid dose for 2–3 days; and that if the child is vomiting or has diarrhoea, hydrocortisone should be given by injection until the medication can be tolerated by mouth.

Biochemical monitoring is important in CAH. Different clinics monitor their patients' progress in different ways. Serum 17OHP is subject to diurnal variation, so some clinics ask patients to collect a series of dried blood spots on filter paper across the 24 h and to mail them to the laboratory. Others compromise and measure only an early morning 17OHP, but also measure plasma renin activity. Decisions about changing doses of hydrocortisone and fludrocortisone are then made using the collated clinical and biochemical information. It is undesirable to completely suppress serum 17OHP, even to the normal range, because adrenal androgens are more readily suppressed than 17OHP and because over-treatment will retard linear growth and cause excessive weight gain. It has been recommended (Hughes 1990b) that early morning 17OHP levels should be maintained in the range 30–70 nmol/L and that the dose of hydrocortisone should be 12–15 mg/m^2/day in divided doses. The dose of fludrocortisone is generally in the range 0.1–0.15 mg/day and is adjusted to maintain plasma renin activity within the normal range.

6.2.1.5 Gender Identity and Sexual Behaviour in 46,XX Cases of CAH

All girls with the classic form of 21-hydroxylase deficiency have had prenatal exposure to levels of adrenal androgens higher than for girls without CAH, some have had additional postnatal exposure to excess androgens and some have experienced severe dehydration and salt depletion after birth. Some neuropsychological effects have been reported in a number of studies (Kelso et al. 2000; Hines et al. 2004; Berenbaum 2001). Prepubertal girls with CAH exhibit tomboyish behaviour (Hall et al. 2004). After puberty has started, some girls with CAH experience gender dysphoria (occasionally severe; Meyer-Bahlburg et al. 1996) and same-sex attraction (Dessens et al. 2005; Wisniewski et al. 2000; Meyer-Bahlburg et al. 2008). Many women with CAH abstain from sexual relations (Mulaikal et al. 1987) and fertility rates for the classic forms of CAH are low, being lower for the salt-losing form than for the simple virilising form (Jaaskelainen et al. 2001; Meyer-Bahlburg 1999).

Bilateral Adrenalectomy in the Treatment of CAH

Management of some patients with CAH can be very difficult with conventional management. For example, it may be impossible to achieve suppression of hyperandrogenism without causing obesity or other symptoms of hypercortisolism. In 1996, bilateral adrenalectomy was proposed (Van Wyk et al. 1996) as a treatment to consider in such situations, especially when the patient has a null mutation in the CYP21A2 gene. Subsequent experience in 18 patients followed up for an average post-operative duration of 59 months supports the view that these selected patients generally benefited by the procedure (Van Wyk and Ritzen 2003).

6.2.2 11β-Hydroxylase Deficiency

This is the second most common type of CAH after 21-hydroxylase deficiency, accounting for 5–8% of cases of CAH (except in the Middle East, where it is more prevalent; Rosler et al. 1992) and like that condition, it causes virilisation of a female foetus. The nature of the biochemical defect was first discovered in 1956 (Bongiovanni and Eberlein 1956). It is inherited as an autosomal recessive condition. The 11β-hydroxylase enzyme is needed for the conversion of 11-deoxycortisol to cortisol and of 11-deoxycorticosterone to corticosterone. The accumulation of 11-deoxycorticosterone results in arterial hypertension and sometimes clinically significant hypokalaemia, but paradoxically, infants with this condition may show transient salt wasting before the commencement of treatment (al-Jurayyan 1995) and an incorrect diagnosis of 21-hydroxylase deficiency can be made. The hypertension can develop soon after birth and be severe enough to cause seizures (Rosler et al. 1988). The CYP11B1 (OMIM # 610613) gene is located on chrosome 8q21. Prenatal virilisation occurs in the classic form, and expression studies have shown that there is little or no enzyme activity present in these cases. There is, in addition, a non-classic form of 11β-hydroxylase deficiency, in which enzyme activity may be 25–40% of wild type (Parajes et al. 2010). The diagnosis of 11β-hydroxylase deficiency is established by measuring both 17-hydroxyprogesterone and 11-deoxycortisol in blood and through the detection of excessive amounts of tetrahydro-11-deoxycortisol in the urine by GC-MS analysis. Treatment with hydrocortisone suppresses ACTH and as the levels of deoxycorticosterone fall, blood pressure returns to normal. Treatment is monitored by tracking serial measurements of 11-deoxycortisol in the blood, along with linear growth and blood pressure measurements. Occasionally the hypertension can be very resistant to conventional treatment with steroids and anti-hypertensive drugs; bilateral adrenalectomy has been successfully used in several cases (Kacem et al. 2009; John et al. 2009).

6.2.3 3β-Hydroxysteroid Dehydrogenase Deficiency

This is a rare type of CAH which can cause ambiguous genitalia in both male and female fetuses. Mutations are found in the 3β-HSD Type 2 gene (OMIM # 201810; locus chromosome 1p13.1). The enzyme is required for the conversion of pregnenolone to progesterone, 17-hydroxypregnenolone to 17-hydroxyprogesterone and dehydroepiandrosterone to androstendione in the adrenal glands and gonads. In genetic males, the reduction in testosterone secretion by the testes results in under-development of the male genitalia. In the female, the over-production of dehydroepiandrosterone by the adrenals causes clitoral enlargement and labial fusion. Not all patients have ambiguous genitalia; some are salt-losing in the neonatal period but have normal genitalia. Most patients with the classic form of the condition have both ambiguous genitalia and are salt-losing (Simard et al. 2002). Biochemically, 3β-HSD deficiency is characterised by elevated levels of serum 17-hydroxypregnenolone and DHEAS (Lutfallah et al. 2002). Because 17OHP and androstenedione levels are also increased, mis-diagnosis of 21-hydroxylase deficiency can occur (Nordenstrom et al. 2007).

6.2.4 P_{450} Oxidoreductase Deficiency

In this rare form of CAH, female infants are born with ambiguous genitalia, some males have hypogonadism, and some infants have craniosynostosis and other skeletal features of Antley-Bixler syndrome (OMIM # 201750). The biochemical profile suggests a combination of 21-hydroxylase deficiency and 17α-hydroxylase deficiency (Fujieda and Tajima 2005), with impaired cortisol biosynthesis, increased ACTH and 17-hydroxyprogesterone and impaired androgen biosynthesis. Paradoxically, androgens are produced by an alternative pathway and in some cases, both the mother and her female foetus were simultaneously virilised (Fluck et al. 2008) (as also occurs in placental aromatase deficiency). Mutations are found in the POR gene (OMIM # 124015; locus chromosome 7q11.12).

6.2.5 17α-Hydroxylase Deficiency

In common with 11β-hydroxylase deficiency, 17α-hydroxylase deficiency causes the accumulation of mineralocorticoid precursors (in this case, corticosterone and deoxycorticosterone) and arterial hypertension; it also causes a reduction in cortisol biosynthesis and an increase in ACTH secretion. Unlike 11β-hydroxylase deficiency, however, 17α-hydroxylase deficiency is associated with a defect in androgen synthesis, so that genetic males as well as females may be born with female or ambiguous genitalia. The ovaries are unable to make oestrogens, because the pathway is via the aromatisation of testosterone. In either sex, the diagnosis may be delayed until the second decade, when puberty fails to occur; the discovery of the hypertension, associated with hypokalaemia is the vital clue. The enzyme that is deficient is actually steroid 17-mono-oxygenase, which has both 17α-hydroxylase and 17,20-lyase activities. Treatment of a 46,XX patient would be with a glucocorticoid (which will usually correct the hypertension) and the combination of oestrogen and a progestogen. Mutations have been found in the CYP17A1 gene (OMIM # 609300; Rosa et al. 2010; Tian et al. 2009). A high prevalence of the condition is found in Mennonite populations in Brazil, Canada and the Netherlands (Imai et al. 1992; Miller 2004; Costa-Santos et al. 2004) but it is rare elsewhere. Some virilization is possible at puberty in 46,XY cases.

6.2.6 Lipoid Congenital Adrenal Hyperplasia

This condition gets its name from the appearance of the adrenal glands, which are convoluted, lipid-laden and bright yellow. The gonads in both males and females are also affected. No adrenal or gonadal steroids are produced in the most severe cases, so that the phenotype is always female or ambiguous. The underlying cause is a mutation in the gene encoding the steroid acute regulatory protein (OMIM # 201710), which is needed for the transport of cholesterol, the substrate for all steroid biosynthesis, to the inner mitochondrial membrane (Bose et al. 1996; Arakane et al. 1998). Cholesterol accumulates in the cytoplasm and has a toxic effect on the cell. In classic lipoid CAH, a female infant will have a hyperpigmented appearance and develop hypoglycaemia soon after birth; salt wasting becomes evident towards the end of the first week. The urine steroid profile on GC-MS analysis is flat. Milder phenotypes have been reported, some presenting only as familial glucocorticoid deficiency (Baker et al. 2006). A Japanese report (Fujieda et al. 1997) describes a 46,XX patient with lipoid CAH who entered puberty spontaneously and women who have had pregnancies have been reported (Khoury et al. 2009). If correctly diagnosed and treated with glucocorticoid, mineralocorticoid and later sex hormone replacement, the condition has a good prognosis.

6.3 Steroidogenic Factor-1 Deficiency

In its most severe form, deficiency of a nuclear receptor, steroidogenic factor-1 (SF-1; also known as NR5A1) results in failure of development in both the adrenals and the gonads (Achermann et al. 1999). There are, however, some milder phenotypes. In females, it can manifest as primary ovarian failure without evidence of glucocorticoid deficiency (Lourenco et al. 2009). The reverse is also possible: a girl with functioning ovaries may have glucocorticoid deficiency (Biason-Lauber and Schoenle 2000).

6.4 46,XX Gonadal Dysgenesis

A familial form of 46,XX gonadal dysgenesis due to a mutation in the FSH receptor gene was reported from Finland (Tapanainen et al. 1998; Aittomäki et al. 1996). Ovarian dysgenesis and premature ovarian failure may also occur in SF-1 deficiency, as described above. The possibility of sex chromosome aneuploidy needs to be borne in mind; absence of low level aneuploidy in peripheral blood does not exclude the possibility of mosaicism in the ovary. Sex chromosome micro-array analysis facilitates the detection of X-chromosomal deletions and rearrangements.

6.5 Müllerian Duct Agenesis

Vaginal agenesis, usually associated with absent uterus and proximal fallopian tubes, but with normal ovarian development, is found in approximately 1 in 4,000–5,000 female births. This is sometimes called the Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome. There is an increased risk for associated renal (40%), skeletal (mostly vertebral 10%) and abdominal wall abnormalities. There may be a vaginal opening present with a hymen, although in a one-fourth of these there may be a hymenal anomaly present in the form of a cribriform, septate or arcuate hymen. The hymen will be absent in about one-third and in these girls there is likely to be an associated absent kidney. Some degree of Müllerian anomalies is reported to occur in 7% of the female population (Vallerie and Breech 2010). Familial clusters have been reported and although a great deal of attention has been focused on the *WNT4* gene, mutations in that gene appear rarely to be involved, except perhaps in a small subset of cases with hyperandrogenism (Biason-Lauber et al. 2007).

Successful lengthening of the vagina may require surgery, but can also be achieved by a non-surgical approach using dilators or sexual activity with an understanding partner (Kimberley et al. 2011). Women with vaginal agenesis will benefit from psychological support (Bean et al. 2009).

6.6 46,XX Testicular DSD

One in every 20,000 males with testes has a 46,XX karyotype. In the majority, a translocation of *SRY* to the tip of one of the X-chromosomes has occurred. In SRY-negative cases (Kolon et al. 1998), there is intense research activity to try and identify mutations in other genes capable of regulating testicular development. Some evidence points to *SOX3* (Sutton et al. 2011). There are some phenotypic similarities between 46,XX men and those with Klinefelter syndrome, but 46,XX men tend to be shorter than men with KS(Vorona et al. 2007). Both syndromes are associated with poor semen volume and oligospermia (Aksglaede et al. 2009).

6.7 46,XX Ovo-Testicular DSD

Ovo-testicular DSD is a specific type of gonadal dysgenesis characterised by the presence of ovarian follicles and seminiferous tubules in the gonads of the one individual and in all populations studied, the 46,XX karyotype is the one most frequently found. A more complete discussion is found in Chap. 8.

6.8 Cloacal Exstrophy and Bladder Exstrophy

These complex anomalies affect the lower abdominal wall and perineum, leading to abnormal external genital development. A detailed description is found in Chap. 9.

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46,XY DSD

7

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The karyotypic group with the greatest diversity in clinical spectrum of DSD is in individuals who have a 46,XY sex chromosome complement. Atypical sex development can occur through interruption of any part of testicular development, the hormonal hypothalamic-pituitary-gonadal axis, or morphogenesis of the urogenital region. These three broad groups of DSD aetiology are termed gonadal dysgenesis, hormonal dysfunction, and abnormal morphogenesis respectively (Table 7.1).

7.1 Clinical Presentation

DSD in a 46,XY individual can present within a wide clinical spectrum from, absence of development of secondary sex characteristics in an adolescent boy, to hypospadias or ambiguous genitalia at birth, or primary amenorrhoea in an adolescent child with a complete female phenotype. The variation in clinical presentation is due to two factors: the degree of disturbance of androgen production or action, and the temporal point at which this disturbance occurs during sex development.

The anatomic presentation is defined by the level of virilisation of the external genitalia, the morphology of the internal genitalia, and the presence or absence of Müllerian structures (uterus, fallopian tubes, cervix and upper vagina). Numerous clinical rating scales exist for external genital virilisation, with scales developed for general use (External Masculinisation Scale), and specifically for androgen insensitivity (Quigley Scale) and virilisation of an XX individual (Prader Stage) (Prader 1954; Ahmed et al. 2000; Quigley et al. 1995). In clinical practice the experience of the authors is to use the Prader scale for all DSD; however the EMS is a more detailed scale in academic use (Fig. 7.1). The distinguishing feature of the Quigley scale is that it defines two forms of complete androgen insensitivity syndrome (CAIS) – presence of female external genitalia with and without secondary sex characteristics.

Complete absence of androgen action, due to any cause, from the time of early fetal development results in a child with a typical female external phenotype. Absence of androgen action at much later time points can cause failure of puberty in an adolescent boy..

Partial action of androgen during fetal development causes hypospadias – a urethral opening on the ventral aspect of the penis at the glans, midshaft, penoscrotal or perineal regions depending on the level of androgen dysfunction. Micropenis, where the stretched penile length at birth is less than 2 cm, can also occur with limited androgen action (Lee et al. 1980). Cryptorchidism or undescended testes, can result from developmental androgen deficiency, and small or absent testes suggests testicular dysgenesis (Hutson et al. 2010)

Urinary tract anomalies occur where there is hypospadias requiring repair for normal urine flow, and also in more significant under-virilisation where there can be vaginal confluence with the urethra, leading to formation of a single urogenital sinus (Vidal et al. 2010).

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Table 7.1 Causes of 46,XY DSD

Gonadal dysgenesis	Partial gonadal dysgenesis
	Mixed gonadal dysgenesis
	Complete gonadal dysgenesis
	Testicular regression syndrome
	Ovo-testicular DSD
	(due to gene mutations in SF1, WT1)
Androgen dysfunction	
Gonadotrophin dysfunction	Isolated gonadotrophin deficiency
	Multiple pituitary hormone deficiency
	LH receptor defect
Steroidogenesis dysfunction	Steroidogenic acute regulatory protein
	Cholesterol side-chain cleavage enzyme
	17α-hydroxylase deficiency
	17,20-lyase deficiency
	3β-hydroxysteroid dehydrogenase deficiency-2
	P450 oxidoreductase deficiency
	Cytochrome b5 deficiency
	17β-hydroxysteroid dehydrogenase-3 deficiency
	5α-reductase-2 deficiency
Androgen insensitivity	Partial androgen insensitivity syndrome (mild, moderate and severe)
	Complete androgen insensitivity syndrome
	Persistent Müllerian duct syndrome
	Bladder and cloacal exstrophy
MIS/AMH dysfunction	
Non-hormonal anatomical disorders	

Surgical repair of the latter prevents retrograde urine flow into the vagina. As the degree of urinary tract anomaly does not correlate well with external genital virilisation, a further classification scale has been devised to define any urologic abnormalities (Rink et al. 2005).

In 46,XY DSD, Müllerian structures may be present or absent. If Sertoli cells do not develop in the embryonic testis, Müllerian inhibiting substance/anti-Müllerian hormone (MIS/AMH) is not released and Müllerian structures will remain as the female genital tract. In 46,XY individuals with functioning Sertoli cells and AMH receptors, the Müllerian structures regress, as is usual. It is essential to determine if Müllerian structures are present in any patient with 46,XY DSD, as this will have a bearing on future fertility options for those raised female, or will need to be eventually surgically removed for those raised male. The morphology of any Müllerian structures can be assessed through a grading system of the American Fertility Society. The level of hypoplasia is classified as vaginal, cervical, fundal, tubal, or combined (American Fertility Society 1988).

Cryptorchidism occurs where the multimodal mechanisms controlling testicular descent are impaired. These mechanisms include roles of androgen, molecular factors such as INSL3 and GREAT, and mechanical factors associated with the abdominal wall (Foresta et al. 2008; Hutson et al. 2010).

The 46,XY ovo-testicular DSD are discussed in Chap. 8 on “Mixed sex chromosome DSD and ovo-testicular DSD.”

7.2 Incidence

Due to the varied clinical presentation of 46,XY DSD, a comprehensive incidence for the group of disorders is not known. The most common presentation, hypospadias, is understood to occur in 1 in 125 male births, with varying reports of a rising incidence thought to be due to environmental endocrine disruptors (Paulozzi 1999; Fisch et al. 2010). More severe clinical presentations carry a greater likelihood of an underlying genetic disorder, and are less common; complete androgen insensitivity, for example, has an incidence of 1:20,000 people (Bangsboll et al. 1992).

In addition to the wide spectrum of clinical presentation, 46,XY DSD are further complicated by difficulty in ascertaining a clear diagnosis. Despite thorough hormonal and molecular-genetic investigations, an accurate diagnosis is consistently unable to be achieved in the majority of patients with 46,XY DSD (Hughes 2008; Bhullar et al. 2011). Much research effort continues to be directed to understanding the aetiology of 46,XY DSD so that this situation can be improved.

7.3 Complications

Accurate diagnosis allows for improved clinical management of 46,XY DSD and its complications, including gonadal germ cell cancer risk, as well as risks of infertility, sexual dysfunction and psychosocial

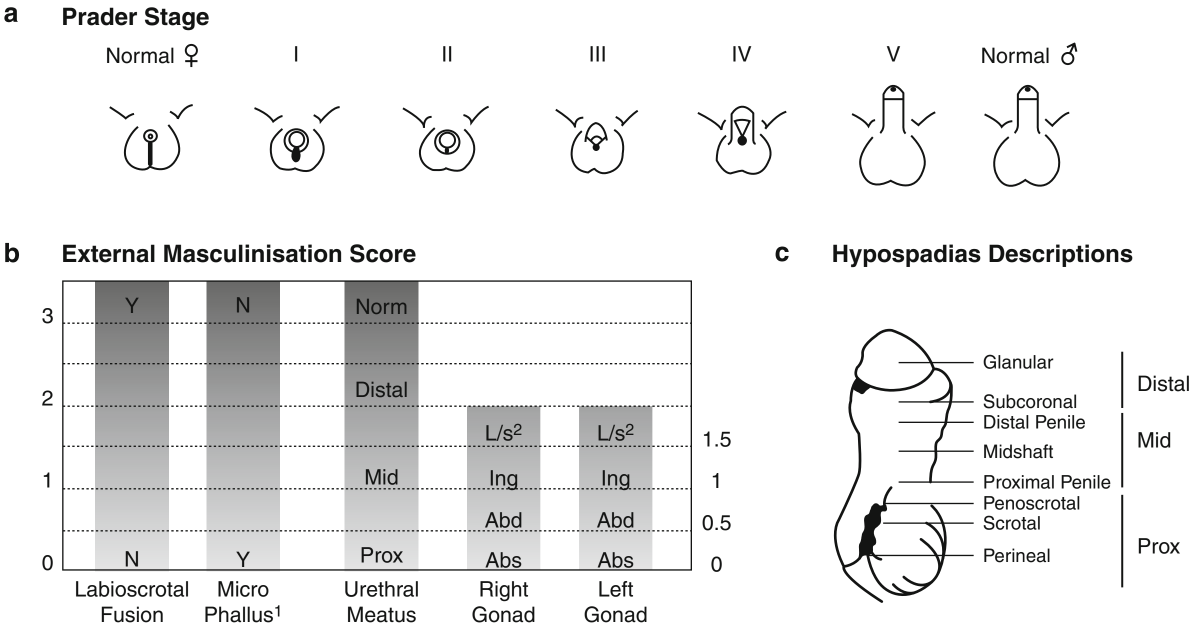

Fig. 7.1 Assessment of external genitalia. (**a**) Prader Stage. (**b**) External masculinisation score. (**c**) Classification of hypospadias (Reproduced with permission from Ahmed and Rodie 2010)

concerns. The magnitude of each of these risks varies according to both the underlying diagnosis and the severity of underlying disease.

7.3.1 Germ Cell Tumours

The risk of gonadal germ cell cancer is of primary importance in 46,XY DSD management. Broadly, germ cell tumours occur with increased frequency in testes with impaired development and presence of Y-chromosomal material. The search for associated oncogenes on the Y chromosome has revealed candidate genes, such as GBY and TSPY (Cools et al. 2006). Germ cell cancer is the result of Y chromosome-mediated up-regulation of genes associated with pluripotentiality, such as PLAP, OCT3/4, c-KIT and its ligand, stem cell factor, in the poorly matured germ cells of DSD testes. Germ cells with arrested development in the DSD testis and in the presence of the Y chromosome undergo transformation into one of two pre-malignant states, termed carcinoma-*in-situ* and gonadoblastoma. Malignant transformation can occur toward any of the various germ cell cancers due to the pluripotential capacity; these cancers include seminoma, or non-seminomatous teratoma, yolk sac tumour or choriocarcinoma.

Carcinoma-*in-situ* testis and gonadoblastoma are early forms of neoplasia in which there is no invasion of surrounding tissue by the pre-malignant cells. Carcinoma-*in-situ* cells, as germ-cell cancer precursors, are situated within the spermatic tubules and appear gonocyte-like, with abundant cytoplasm. Gonadoblastoma cells comprise a proliferative admixture of immature germ cells and sex cord-stromal cells within the spermatic tubules. In this state, differentiation of carcinoma-*in-situ* or gonadoblastoma from the appearance of simple maturational delay in a DSD gonad can be difficult, and histological staining for markers of pluripotentiality such as AP-2γ or OCT3/4 is suggested (Fig. 7.2). In individuals at high risk for germ-cell cancer, testicular biopsy should be analysed for pre-malignant lesions after the onset of puberty if the testes have been left in situ. It is currently thought that all carcinoma-*in-situ* cells and 50% of gonadoblastoma cells will eventually undergo malignant transformation (Looijenga et al. 2007).

The germ-cell cancer risk in 46,XY DSD has been defined in a diagnosis-specific manner according to currently available follow-up data. It is reported to be

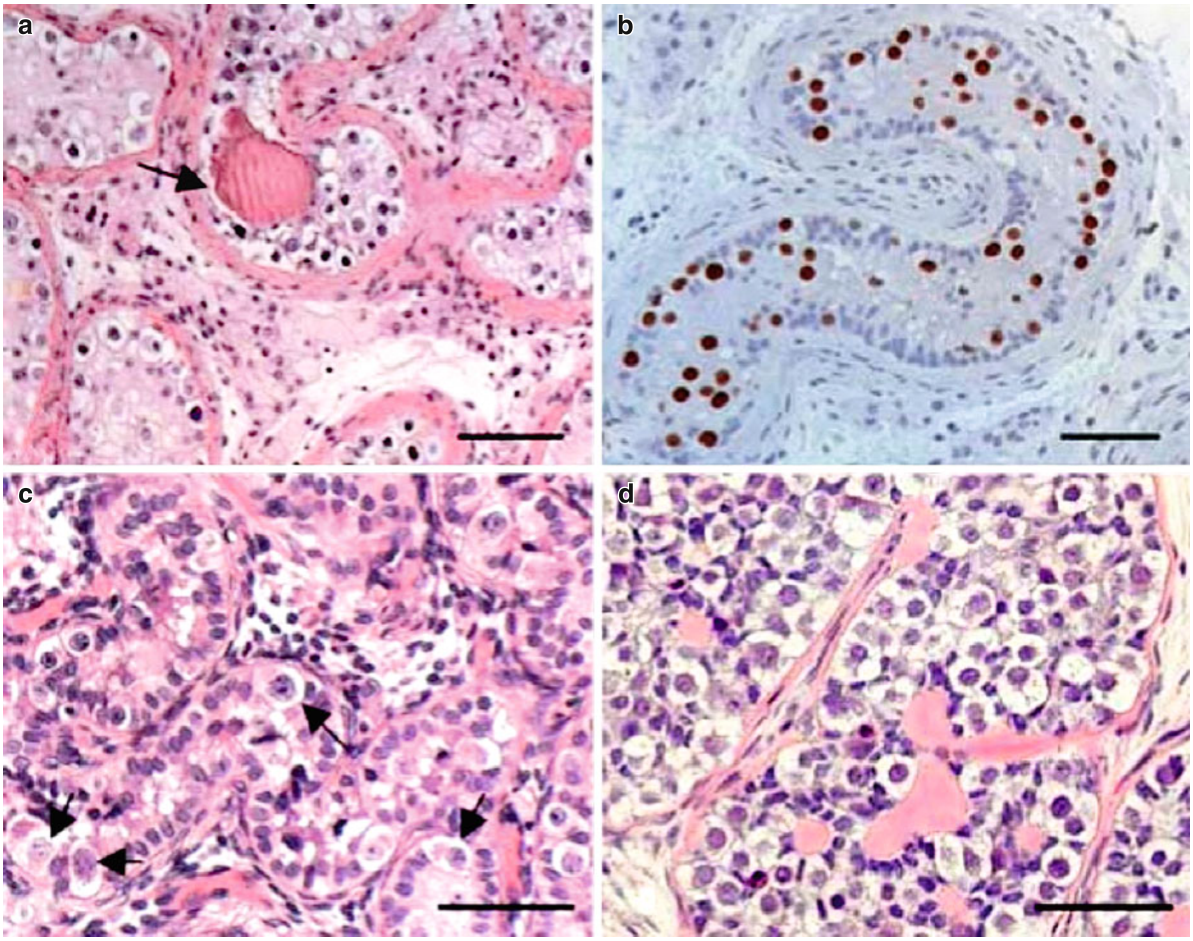

Fig. 7.2 Histological appearance of preinvasive changes. (**a**) Carcinoma in situ (CIS) in the contralateral testis of an adult man with a testicular germ cell cancer. *Arrow* indicates a microlith. (**b**) CIS cells in a tubule with undifferentiated Sertoli cells; CIS cells stained for AP-2. (**c**) *Arrow* indicates CIS in the testis of a prepubertal girl with mixed gonadal dysgenesis 46,XY/45,X. (**d**) Gonadoblastoma in an adolescent boy with mosaicism for sex chromosome aneuploidy (Scale bar = 50 m) (Reproduced with permission from Rajpert-de Meyts and Hoei-Hansen 2007)

up to 60% for some diagnoses, such as those associated with WT1 mutations (Looijenga et al. 2007).

Testicular germ-cell cancers are classified into seminomatous and non-seminomatous tumours. The former arise purely from the primordial germ-cell lineage and the latter represent pluripotential differentiation along various lineages, including teratoma, choriocarcinoma, and yolk-sac carcinoma and embryonal carcinoma. The overall 5-year survival rate is now over 95%; however late tumour recurrence is reported (Oldenburg et al. 2006). Seminomatous tumours are sensitive to adjuvant radiotherapy after resection, and non-seminomatous tumours are sensitive to chemotherapy. Tumour staging allows stratification of good- and poor-risk patients. Poor risk occurs in 10–25%, and is associated with high serum tumour markers, metastases, and mediastinal, non-seminomatous tumours (Bosl and Motzer 1997).

Testicular germ-cell cancers typically present with a mass or a painless swelling of one testis, though pain can be a presenting feature in a minority. Ultrasonography is the initial investigation tool and under ideal conditions can localise testicular lesions as small as 1–2 mm in diameter, especially ones that are calcified. Serum tumour markers produced by non-seminomatous tumour types include α-fetoprotein and human chorionic gonadotrophin β-subunit. Further anatomical imaging by MRI or CT scan along with chest X-ray can define the anatomy of the tumour, and any regional lymphadenopathy or distant metastases.

Table 7.2 Risk of type-II germ cell tumors in the various categories of disorders of sex development (DSD) patients, classified into high-, intermediate-, low- and no-risk groups

Risk group	Disorder	Malignancy risk (%)	Recommended action	Studies (*n*)	Patients (*n*)
High	GD[a] (+Y)[b] intra-abdominal	15–35	Gonadectomy[c]	12	>350
	PAIS non-scrotal	50	Gonadectomy[c]	2	24
	Frasier	60	Gonadectomy[c]	1	15
	Denys–Drash (+Y)	40	Gonadectomy[c]	1	5
Intermediate	Turner (+y)	12	Gonadectomy[c]	11	43
	17β-HSD	28	Monitor	2	7
	GD (+Y)[c]	Unknown	Biopsy[d] and irradiation?	0	0
	PAIS scrotal gonad	Unknown	Biopsy[d] and irradiation?	0	0
Low	CAIS	2	Biopsy[d] and ?	2	55
	Ovotestis DSD	3	Testis tissue removal?	3	426
	Turner (−Y)	1	None	11	557
No (?)	5α-reductase	0	Unresolved	1	3
	Leydig cell hypoplasia	0	Unresolved	2	

CAIS complete androgen insensitivity syndrome, *17β-HSD* 17β-hydroxysteroid dehydrogenase deficiency, *PAIS* partial androgen insensitivity syndrome

[a] Gonadal dysgenesis (including not further specified, 46XY, 46X/46XY, mixed, partial, complete)

[b] GBY region positive, including the *TSPY* gene

[c] At time of diagnosis

[d] At puberty, allowing investigation of at least 30 seminiferous tubules, with diagnosis preferably based on OCT3/4 immunohistochemistry

Reproduced with permission from Looijenga et al. (2007)

Mitigation of the germ-cell cancer risk can occur through various means, dependent on the risk associated with the underlying DSD aetiology. In the situation of simple hypospadias and cryptorchidism, there is a two- to four-fold increased risk of testicular germ-cell cancer in early adulthood and regular, thorough testicular self-examination is recommended (Schnack et al. 2010). In partial androgen insensitivity syndrome (PAIS) or mild gonadal dysgenesis, where the child is raised male and the testes are secured in a scrotal position, the testes may be left in situ with strict cancer surveillance. Biopsy and analysis for pre-malignant lesions at commencement of puberty, subsequent regular testicular examination, and annual tumour marker analysis with intermittent ultrasound are suggested for follow-up of patients at long-term risk of testicular germ-cell cancer (Looijenga et al. 2007; Schmoll et al. 2010). In individuals with high risk of germ-cell cancer, such as 46,XY complete gonadal dysgenesis (where cancer risk approximates 30%), or PAIS with intra-abdominal gonads (where cancer risk approximates 50%), risk-reducing prophylactic gonadectomy is recommended (Looijenga et al. 2007) (Table 7.2). As absolute germ-cell cancer risk defines the strategy for risk reduction, including decision on gonadectomy, further work to clarify both diagnostic grouping and diagnosis-specific cancer risks is important.

7.3.2 Infertility

Infertility to some degree is a common complication of 46,XY DSD. For individuals with mild hypospadias or cryptorchidism, fertility may be possible without the need for assisted reproductive technology. Successful attempts for paternity occur in 93% men with normally descended testes, 90% in men with unilateral cryptorcidism, and 65% in men with bilateral cryptorchidism (Lee and Coughlin 2001). For other forms of 46,XY DSD, fertility may be more significantly reduced. Advances in assisted reproduction continue, and now allow for successful use of germ cells developed to the level of round spermatids in intra-cytoplasmic sperm injection (Tesarik et al. 1995). Unfortunately, in many individuals with DSD the developing germ cells do not even reach this minimal stage of development and therefore the sperm cannot be used. Testicular biopsy can be analyzed for germ cell and sperm development in addition to cancer risk.

Should there be viable sperm in a gonad which is to be treated prophylactically or therapeutically for germ cell cancer, sperm salvage, and storage via cryopreservation should be offered. Other options for parenting involve gamete donation, or adoption/fostering.

In the case of female individuals with 46,XY complete gonadal dysgenesis, the presence of Müllerian structures allows consideration of embryo implantation and carriage of pregnancy to term.

7.3.3 Hormonal and Sexual Function

Testicular failure in male 46,XY DSD individuals can occur prior to or after puberty, or may be induced by prophylactic gonadectomy. Regular hormonal assessment is therefore important, and patients should be counselled on the symptoms of androgen deficiency.

Puberty can be induced with oral (testosterone undecanoate 40 mg daily), intramuscular (testosterone esters 50–100 mg monthly), or transdermal testosterone (2.5 g daily), using a gradually increasing dose to adult replacement over 6–12 months (Ambler 2009). Patients should be counselled on the importance of continuous testosterone replacement for the purposes of metabolic and bone health, in addition to subjective wellbeing. Metabolic parameters and bone densitometry should be considered for individuals who have intermittent adherence to hormone replacement.

Long-term follow-up of men with micropenis indicate that genital and sexual function can be satisfactory when raised male; however there may be dissatisfaction with body image (Wisniewski et al. 2001).

In female 46,XY DSD individuals, risk-reducing gonadectomy has often led to the requirement for hormone replacement therapy with or without induction of puberty from age 12. Oestrogen can be commenced in oral (oestradiol valerate 25 mcg daily) or transdermal (oestradiol 25 μg/day) forms, increasing the dose to adult replacement over 2 years, and progestogens are not indicated unless there is a uterus (Hewitt and Warne 2009; de Muinck Keizer-Schrama 2007). Induction of secondary sex characteristics should occur slowly in females; otherwise the breasts may develop a somewhat tubular shape if oestrogen dose is increased too rapidly.

Women with 46,XY DSD and absence of Müllerian structures will only have presence of the lower 1/3 of the vagina (sometimes much less than that); they may require serial vaginal dilatation prior to sexual debut. Graduated solid dilators are applied with pressure against the vaginal dimple daily for a minimum of 30 min after a warm bath. Functional success is reported in approximately 90% of women with vaginal agenesis after 18 months (Gargollo et al. 2009). In individuals in whom non-surgical treatment fails, creation of a neovagina can occur through use of skin graft or bowel tissue. Issues relating to clitoroplasty are discussed in Chap. 6 on 46,XX DSD and Chap. 17.

7.3.4 Urinary Function

Depending on the severity of under-virilisation, multiple surgical procedures may be required to assist integrity and function of the urinary tract. Long-term follow-up of males who had had surgery for a DSD demonstrated a high prevalence of persisting urological difficulties, including wetting (25%), spraying of urine (31%), and recurrent infections (25%) (Warne et al. 2005). Urological dysfunction and management is discussed further in Chap. 17 on Surgical Management.

7.3.5 Psychosocial Concerns

A 46,XY DSD diagnosis is a significant stressor for both the affected individual, their family and their partners. Long-term psychosocial support is recognized as an essential part of medical care; however it remains the realm in which care providers are thought to perform most poorly as reported by patients (Jones et al. 2009; Crawford et al. 2009). In long-term follow-up, most patients report a good quality-of-life outcome (Warne 2008; Warne et al. 2005); however in some individuals, distress can lead to significant functional impairment, with risk of self-harm (Schutzmann et al. 2009).

With limited evidence to guide gender assignment at birth, some individuals will experience gender dysphoria or will identify with a gender contrary to the one in which they were raised. Long-term outcome studies from small cohorts indicate that gender dysphoria can exist regardless of sex of rearing for many diagnoses, including partial gonadal dysgenesis and PAIS, and even CAIS (Migeon et al. 2002; Veale et al. 2010; T'Sjoen et al. 2011). It is possible that gender dysphoria, and to a lesser extent gender reassignment, may be inevitable for a group of persons with DSD; some individuals identify with an "in-between" gender, or even no gender. These are significant issues for individual self-understanding, and unhindered access to psychological support is essential.

Whilst traditionally, significantly under-virilised 46,XY DSD infants were assigned a female gender due to concerns about adequate sexual function, this approach is now being reconsidered. Gender assignment in 46,XY DSD with some evidence of functional testes has gradually shifted toward male in recent times (Diamond and Beh 2008). Reasons for this are multiple, and include the understanding that most individuals as adults identify with their original sex of rearing; men with micropenis are understood to have potential for satisfactory sexual outcomes; and feminising genitoplasty involves the irreversible removal of erectile tissue, which may be missed in an individual later identifying as male. Furthermore, evidence is emerging that individuals with a 46,XY karyotype and some level of prenatal virilisation, in addition to potential for spontaneous or induced pubertal virilisation, can have difficulty accepting a female gender assignment (Reiner and Gearhart 2004). Male assignment is now considered for children with 46,XY karyotype and micropenis, 17β-hydroxysteroid dehydrogenase (17β-HSD3) deficiency, 5α- reductase-2 deficiency, bladder exstrophy, or diagnoses consistent with androgen responsiveness (Mieszczak et al. 2009; Hughes et al. 2006). Female assignment is increasingly reserved for markedly under-virilised 46,XY DSD patients, as in bilateral severe gonadal dysgenesis and retained Müllerian structures, or severe partial (PAIS) or complete androgen insensitivity syndrome (CAIS).

7.4 Genetic Counselling and Disclosure

Many causes of 46,XY DSD arise *de novo*, and lead to infertility in the affected individual, so there is a low risk of recurrence in a family. Others can be inherited in an X-linked, autosomal recessive or even autosomal dominant fashion. Genetic counselling should be provided regarding testing of extended family members, risk of recurrence in future offspring of the parents, and to the affected individual themselves when they are able to comprehend their DSD aetiology.

Disclosure of the diagnosis of 46,XY DSD should occur in a staged and developmentally appropriate manner, with the aim for open and complete disclosure including explanation of complication risks by the completion of puberty (see Chap. 20).

7.5 Undefined 46,XY DSD (Hypospadias and Cryptorchidism)

DSD due to milder forms of hypospadias represent a large patient group, with an incidence of 1 in 125 live male births, thought to be arising due to the increasing effects of endocrine disrupting chemicals in the environment (Paulozzi 1999; Olesen et al. 2007). Chemicals such as phthalates and bisphenol A are used in manufacturing, and are thought to act by reducing testosterone production antenatally in the developing male fetus (Morales-Suarez-Varela et al. 2011).

The rising incidence of hypospadias has been associated with a rising incidence of cryptorchidism and testicular germ-cell cancer in population-based studies, and the concept of a "testicular dysgenesis syndrome" due to environmental exposures is proposed to explain these increases (Olesen et al. 2007). Some authors doubt this hypothesis and argue that the rising hypospadias incidence may not be real (Fisch et al. 2010). A large study in Denmark found evidence that hypospadias or cryptorchidism increased the relative risk for testicular germ cell cancer by two- to four-fold (Schnack et al. 2010). This risk was increased only in affected individuals and not if there was a family history for disease, supporting the "testicular dysgenesis syndrome" association.

In children with more severe degrees of hypospadias and cryptorchidism, the likelihood of a germ-line genetic mutation is more likely, and investigations to determine aetiology are warranted.

7.5.1 Management

Simple hypospadias can be repaired in a single surgical procedure by a range of techniques to extend the length of the urethra, and can be performed within the first 18 months of life (Jones et al. 2009; American

Academy of Pediatrics 1996). This is because it is thought that parental separation anxiety and disturbance of genital awareness both increase after this time. In infants with micropenis, intramuscular testosterone esters 25 mg monthly for 3 months can be administered to increase penile size prior to surgery. More severe degrees of hypospadias may require multiple-staged surgical repairs, and urinary outflow tract dysfunction may exist.

Cryptorchidism resolves spontaneously over the first 3 months of life in up to 70% of children (Berkowitz et al. 1993). In the absence of resolution, there is mixed opinion on the use of hCG to assist testicular descent, due to limited evidence and unclear distinctions of cryptorchidism aetiology and severity. The effectiveness of hCG is reported to range from 0 to 55% (Henna et al. 2004). In addition, concerns have been raised regarding mild inflammatory infiltrate noted at testicular biopsy after hCG administration in older children; however this may be a normal physiological process associated with the usual FSH and LH surge during early infancy (Hjertkvist et al. 1993). Anecdotally, use of hCG has been noted to be of more success in the subgroup of infants with proven hypogonadotrophic hypogonadism, and in this subgroup the dose of hCG used at our centre is 500 IU intramuscularly weekly for 5 weeks. Lower doses are shown to be as efficacious as higher doses (Forest et al. 1988). The vast majority of cryptorchidism; however, is managed with a reported 95% success rate by surgical orchidopexy (Ritzen et al. 2007). Orchidopexy should be timed to occur at 6–12 months to minimize the risk of infertility and germ cell cancer (Mandat et al. 1994; Hutson et al. 2010).

In the setting of associations with increased risk of testicular germ cell cancer and infertility, it is prudent to arrange follow-up of these boys at the time of puberty to counsel them on testicular self-examination, advice on management of future infertility or testicular failure, and to ensure normal pubertal development.

7.6 46,XY Gonadal Dysgenesis

Gonadal dysgenesis occurs where there is disruption in the testicular developmental pathway toward mature Sertoli and Leydig cells. This developmental pathway involves activation of a developmental gene cascade (See Chap. 1: Sex determination and differentiation). Due to our incomplete understanding of the entire process of human testicular development, causative gene dysfunction cannot be determined for all affected individuals (Bhullar et al. 2011; Hughes 2008).

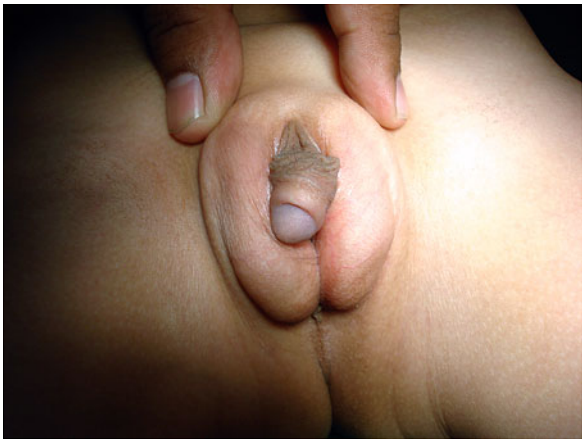

Fig. 7.3 46,XY gonadal dysgenesis with inadequate early androgen production (leading to bifid scrotum and severe chordee of phallus), but improved androgen production later in gestation, leading to growth of the hypospadiac phallus

The diagnosis of gonadal dysgenesis is therefore often based on clinical features and is easier to discern in patients more severely affected than for those mildly affected, where the phenotypic spectrum can overlap with mild disorders of androgenic action. Gonadal dysgenesis of significant severity will lead to small testes with poor androgen-production capacity, presence of Müllerian structures due to absence of sufficient MIS/AMH, and elevated gonadotrophin levels from the time of puberty, due to primary gonadal failure.

Anatomical description is often used to classify disease severity, in addition to the molecular aetiology if available. The group of disorders are therefore classified into partial gonadal dysgenesis (PGD), mixed gonadal dysgenesis (MGD), and complete gonadal dysgenesis (CGD).

In 46,XY partial and mixed gonadal dysgenesis, there is some element of testicular development, evidenced by virilisation of the external genitalia at birth (Fig. 7.3). Mixed gonadal dysgenesis refers to marked asymmetry in gonadal development, with a dysgenetic testis on one side and a streak gonad on the other (Donahoe et al. 1979). It is more often associated with mixed sex chromosome (aneuploidy) DSD but can occur in 46,XY DSD. The level of under-virilisation ranges from mild to severe and Müllerian structures may or may not be present, depending on amount of Sertoli cell function. As MIS/AMH acts in an ipsilateral manner by local exocrine secretion, there can also be asymmetric Müllerian findings such as a hemi-uterus in mixed gonadal dysgenesis..

The 46,XY complete gonadal dysgenesis occurs where there is only streak gonad development, and therefore normal female phenotype with developed Müllerian structures. This disorder is often diagnosed when a karyotype is requested in a girl with delayed puberty, or on antenatally performed karyotype for more routine indications.

The causes of partial or mixed gonadal dysgenesis are loss-of-function mutations in the genes associated with testicular sex determination, or gain-of-function of genes associated with ovarian sex determination. These genes include those at the level of the bipotential gonad such as CBX2, NR5A1, WT1, and GATA4, those at the level of early testis determination such as SRY and DMRT1/DMRT2, and those that act in the testis determination cascade such as SOX9, NR0B1, DHH, ATRX, MAMLD1, TSPYL1, and WNT4.

There are specific phenotypic associations with mutations in some of these genes. Mutations in CBX2 have been reported in one 46,XY female with histologically normal ovaries, an uncommon phenotype (Biason-Lauber et al. 2009). NR5A1 (also called SF1), however, also acts at an early stage of gonadal development but functional mutations have been reported to lead to a spectrum of phenotypes. These range from adrenal and gonadal dysgenesis through isolated gonadal dysgenesis and penoscrotal hypospadias (Lin et al. 2007; Kohler et al. 2009). In contrast to many of the other genes which are involved in gonadal dysgenesis aetiology in infrequent cases, NR5A1 contributes to a large proportion of DSD. It is thought to be associated with approximately 15% of 46,XY partial gonadal dysgenesis and can also cause complete gonadal dysgenesis (Kohler and Achermann 2010; Philibert et al. 2010). WT1 has a tumour suppressor function in addition to its role in organogenesis, and mutations are associated with high risk of germ-cell cancer. There are many isoforms of the WT1 protein, with mutations leading to the (−)KTS isoform resulting in Frasier syndrome, characterised by gonadal dysgenesis, progressive glomerulopathy, and renal failure but not Wilms' tumour. Mutations in WT1 with the (+)KTS isoform lead to Denys-Drash syndrome, with gonadal dysgenesis, diffuse mesangial sclerosis, and frequent development of germ-cell cancer and Wilms' tumour of the kidney (Wagner et al. 2003). The association of Wilms' tumour, aniridia, genitourinary anomalies/gonadoblastoma, and intellectual disability occurs with larger 11p13 deletions which include the WT1 gene, and is termed WAGR syndrome. Mutations in GATA4 are associated with atrial septal congenital heart defects and gonadal dysgenesis, due to the role of this gene in cardiac and testis development (Lourenco et al. 2011).

The key testis-determining factor on the Y chromosome is SRY, and mutations in this gene lead to complete gonadal dysgenesis, currently explaining 15% of 46,XY CGD cases (Cameron and Sinclair 1997). SOX9 up-regulation is thought to be the target of SRY by an as yet undefined mechanism. Mutations in SOX9 lead to gonadal dysgenesis and campomelic dysplasia, due to its role in both gonadogenesis and chondrogenesis. Mutations in regulatory elements surrounding the coding region for SOX9 now indicate that there could be gonad-specific loss of SOX9 function with normal skeletal development in some 46,XY DSD patients (White et al. 2011). These findings for SOX9 regulation are significant, as mutations in regulatory elements of other genes are also likely to lead to gene dysfunction.

NR0B1 (also known as DAX1) leads to 46,XY DSD via an unusual mechanism – that of so-called dosage-sensitive sex reversal. That is, duplications of NR0B1 in a 46,XY individual leads to complete gonadal dysgenesis (Bardoni et al. 1994).

DMRT1 and DMRT2 are associated with gonadal dysgenesis when they are deleted in contiguous distal 9p monosomy disorders; however, dysfunction in a single gene has not yet been reported to cause 46,XY DSD. This suggests that there may be some redundancy between the genes in the region, with a larger deletion required to cause loss of function (Ottolenghi et al. 2000).

DHH mutations are associated with 46,XY partial gonadal dysgenesis and minifascicular polyneuropathy, consistent with the phenotype of the mouse model (Umehara et al. 2000). ATRX mutations are associated with the rare disorder X-linked alpha thalassaemia, mental retardation, and 46,XY DSD (Tang et al. 2011). MAMLD1 is thought to be associated with a less severe 46,XY DSD phenotype and penoscrotal hypospadias (Ogata et al. 2008). TSPYL1 mutations have been associated with sudden infant death with dysgenesis of the testis (Puffenberger et al. 2004).

In addition to loss of function of genes involved in testis development, gain of function in genes involved in ovarian development can also cause 46,XY DSD. This has been reported for WNT4 duplications (Jordan et al. 2003).

7.6.1 Management

The initial management concern for individuals with 46,XY gonadal dysgenesis is the sex of rearing for a child and later gender identity. In the case of 46,XY severe partial or complete gonadal dysgenesis, eventual female gender is the norm for women with a female phenotype with presence of Müllerian structures (McCarty et al. 2006). Where there is evidence of functional testicular tissue (i.e., evidence of virilisation with ambiguous genitalia at birth) consideration to male gender assignment should be made. This is because in the case of female gender assignment, feminising genitoplasty irreversibly removes tissue which may be required later should the individual identify as male, and also that tissue response to androgen should be normal in gonadal dysgenesis, allowing response to testosterone replacement therapy. In all situations regarding difficult gender assignment, ethical considerations should be balanced and weighed (Gillam et al. 2010) (See Chap. 15).

In individuals with persisting Müllerian duct structures who are raised male, the Müllerian tissue can be removed, or conversely ligated and left in situ for removal or otherwise at a later date with the consent of the affected individual. Gonadectomy is recommended for patients with 46,XY DSD and testes which cannot be brought to the scrotum for cancer surveillance. Biopsy as described above should be performed in patients at risk of germ-cell cancer with testes in situ. Regular, intermittent cancer surveillance and monitoring for hormonal testicular failure should occur on a lifelong basis, with fertility assistance as required.

7.6.2 46,XY Testicular Regression Syndrome

Testicular regression syndrome is also variously termed anorchia or vanishing testis syndrome. The common phenotype is the absence of structural testicular tissue in a 46,XY individual with evidence of previously normal testicular function, i.e. testicular regression. Testicular regression can occur antenatally or postnatally, with the eventual clinical finding of absence of palpable testes. There may be a residual nodule on exploration for testicular tissue, containing haemosiderin-laden macrophages or dystrophic calcification (Spires et al. 2000). The aetiology is unknown; the histological findings in residual nodules could be consistent with antenatal testicular torsion and ischaemic damage as a cause. This aetiology would seem more likely for unilateral, rather than bilateral cases. Analysis of candidate gene mutations to explain the aetiology in bilateral cases has revealed an association with NR5A1 mutations in a small proportion of patients (Philibert et al. 2007). Management involves long-term testosterone replacement and fertility assistance

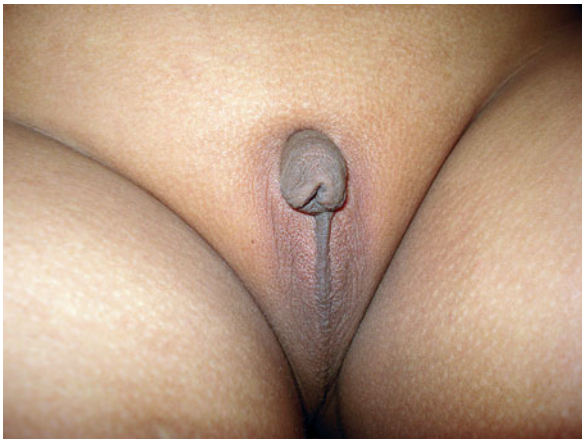

Fig. 7.4 Gonadotrophin deficiency causes failure of growth of the phallus, but early sexual differentiation is normal, as this is controlled by placental hCG

7.7 Gonadotrophin Deficiency or Dysfunction

Aberrant pituitary gland production of gonadotrophins and LH receptor defects result in hypogonadotrophic hypogonadism, which is associated with 46,XY DSD if primary sex development is affected (Fig. 7.4). Gonadotrophin deficiency due to LH or LHRH deficiency in the developing 46,XY fetus typically results in an infant born with micropenis and cryptorchidism. There are a series of genes which can cause hypothalamo-pituitary gondadotrophin deficiency, including the KAL genes, GnRH receptor, FGFR-1 and GPR54 (Iovane et al. 2004). KAL-1 gene mutations are additionally associated with congenital anosmia. Conditions associated with multiple pituitary hormone deficiency will also be associated with gonadotrophin deficiency; these include isolated pituitary disorders associated with gene mutations such as in PIT-1, PROP-1 and HESX-1, and syndromic DSD associations such as Bardet-Biedl, Prader-Willi or CHARGE syndrome (the latter representing **c**oloboma, **h**eart defects, **a**tresia of the nasal choanae, **r**etardation of growth and development, **g**enital abnormalities and **e**ar abnormalities) (Aminzadeh et al. 2010; Rainbow et al. 2005). LH receptor defects are caused by mutations in the LHCGR gene and can present with varying phenotype, from typical female appearance to mild undervirilisation, depending on the severity of LH receptor function loss (Themmen and Verhoef-Post 2002).

Measurement of FSH and LH in the newborn period will reveal absence of the normal early infantile gonadotrophin surge where dysfunction in gonadotrophin synthesis exists. In the case of LH receptor defects, a normal level of FSH is found in association with elevated LH levels, and the cardinal feature is Leydig cell hypoplasia on testicular histology. Müllerian structures will be absent.

7.7.1 Management

Testosterone administration in the infantile period, as described earlier in this chapter, may provide some supplemental penile growth. In this particular group, treatment with hCG to assist testicular descent and increase in testicular volume would be a reasonable consideration. Treatment with pulsatile LHRH, or FSH and hCG, at induction of puberty may assist with testicular development and spermatogenesis (Christiansen and Skakkebaek 2002). Pubertal induction and testosterone replacement will be required from adolescence

In the severe form of LH receptor defect with marked Leydig cell hypoplasia and female phenotype with absence of virilisation, female gender assignment may be considered.

7.8 Disorders of Androgen Biosynthesis

Androgen production occurs according to the same synthesis pathway in the adrenal glands and testes, although some enzymes are testis specific. Dysfunction of an enzyme will lead to accumulation of metabolites prior to the enzyme block, and deficiency of subsequent metabolites.

The level of virilisation of external genitalia is dependent on the severity of the enzyme defect, and can therefore range widely for most causes. Müllerian structures will be absent, except for severe Smith-Lemli-Opitz syndrome, where there is poor basic cholesterol synthesis with an effect on testis development (Kelley and Hennekam 2000).

Unfortunately there are often many terms and gene symbols used to refer to the same protein or enzyme and its coding gene, and we would suggest use of the approved OMIM nomenclature for consistency. These proteins include steroidogenic acute regulatory protein (StAR), cholesterol side chain cleavage enzyme, or 11α-hydroxylase (CYP11A1/P450scc), 17α-hydroxylase and 17,20-lyase (CYP17/P450c17), p450 oxidoreductase (POR), 3β-hydroxysteroid dehydrogenase-2 (HSD 3B2), 17β-hydoxysteroid dehydrogenase-3 (HSD17B3) and 5α-reductase-2 (SRD5A2).

Most of these gene products act in the production of androgen, glucocorticoid, and mineralocorticoid within both the adrenal gland and testis, so there may be an element of cortisol or aldosterone insufficiency requiring replacement therapy in addition to the under-virilisation. Glucocorticoid synthesis reserve should be assessed by an ACTH-stimulation test, and insufficiency treated with stress steroid administration or maintenance and stress steroid replacement. Mineralocorticoid insufficiency results in low sodium and high potassium, with elevated plasma renin activity, and can be treated with fludrocortisone replacement. Testosterone replacement should occur in the standard fashion for individuals who are raised male.

Elevated levels of some metabolites due to the enzyme deficiency can result in phenotypic effects in 46,XY individuals, the most notable are hypertension in 17α-hydroxylase deficiency due to deoxycorticosterone, and partial virilisation in 3β-hydroxysteroid dehydrogenase-2 deficiency due to DHEA excess.

The two enzymes which act at the level of the testes only and which are therefore not associated with glucocorticoid deficiency are 17β-hydroxysteroid dehydrogenase-3, and 5α-reductase-2. Infants born with these enzyme deficiencies can have partially virilised or completely unvirilised genitalia; however a greater consideration to male gender assignment, or

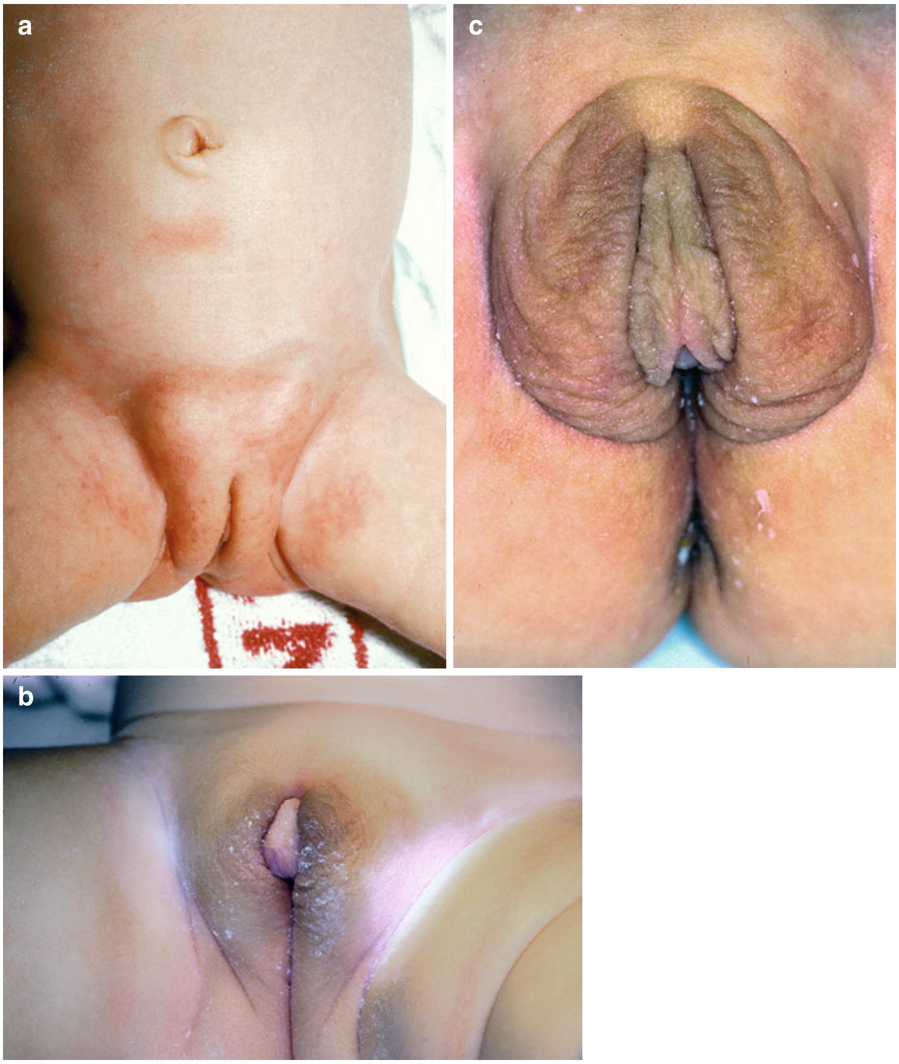

Fig. 7.5 (**a**) Complete androgen insensitivity syndrome (CAIS) showing normal female external genitalia, but visible gonads in the groin, just outside the inguinal canals. The testes have enlarged secondary to loss of negative feedback in gonadatrophin secretion. (**b**) Partial androgen insensitivity syndrome (PAIS), showing minimal virilisation of phallus and genital folds. (**c**) More virilised patient with PAIS, where the genitalia show unfused labio-scrotal folds, but pigmentation and wrinkling is more noticeable and the phallus is much larger than in (**b**)

female gender assignment without feminising genitoplasty, is considered due to the possible occurrence of spontaneous virilisation at puberty associated with male gender identification in 50–70%. In individuals raised female, there can be a transition to identification with the male gender at puberty (Veale et al. 2010; Mieszczak et al. 2009).

7.9 Androgen Insensitivity Syndrome

Dysfunction of the androgen receptor leads to varying degrees of androgen insensitivity and incomplete virilisation of a 46,XY individual. The clinical spectrum ranges from completely phenotypic females with minimal pubic hair to phenotypically normal males with infertility or reduced body hair (Fig. 7.5).

Classification of severity is classically divided into complete androgen insensitivity syndrome (CAIS) and partial androgen insensitivity syndrome (PAIS); however this dualistic division is associated with some problems in clinical practice, which will be discussed.

Complete androgen insensitivity syndrome is defined as total impairment of the androgen receptor leading to unvirilised female phenotype and absence of pubic hair. Testes produce normal or elevated levels of testosterone from puberty if left in situ; testosterone is then aromatised to oestrogen with spontaneous development of female secondary sex characteristics. The testes are usually situated very near to the inguinal canal. The epididymis and vas deferens are usually absent. These individuals are usually diagnosed upon presentation with inguinal hernia in infancy, primary amenorrhoea post puberty, or as an incidental finding on karyotype for other reasons. Gender identity is nearly exclusively female (Hines et al. 2003) and germ-cell cancer risk in CAIS is low at 2% (Looijenga et al. 2007).

A phenotype which resembles complete androgen insensitivity, but where there are trivial signs of virilisation in a classically female individual, occurs in the severe form of partial androgen insensitivity syndrome. Unfortunately, in clinical practice many clinicians incorrectly term this phenotype CAIS, and terms such as "severe partial androgen insensitivity" have been suggested. The distinction from CAIS is important due to a significantly different germ-cell cancer risk; there is a very high risk of 50% with non-scrotal gonads, where gonadectomy is recommended at the time of diagnosis (Looijenga et al. 2007). A compromise in terminology may be warranted for this group in order to assist phenotypic classification in a clinically meaningful manner, by using a term associated with CAIS such as incomplete or near complete androgen insensitivity syndrome. Vaginal dimensions may be less than an unaffected female due to low-level virilisation, and dilatation or surgical management may be required to achieve functionality.

A third group of clinical presentations of androgen insensitivity syndrome involves the under-virilised male, with varying degrees of hypospadias, cryptorchidism, Wolffian duct development or vaginal presence, and sparse chest or facial hair. Testosterone aromatisation leads to problematic gynaecomastia in this group from puberty, which may necessitate mastectomy in a child raised male. Germ-cell cancer risk is as yet undefined in scrotal gonads, however is thought to be less than that for non-scrotal gonads. Sexual dysfunction is high in men in this group compared to unaffected men (Bouvattier et al. 2006). Individuals raised male or female identify with their sex of rearing in the majority, however presence of gender dysphoria exists in up to 30% individuals, including those raised as either sex (Veale et al. 2010; Migeon et al. 2002).

Mild partial androgen insensitivity syndrome can present with distal hypospadias or cryptorchisim, or with a normal male phenotype but gynaecomastia or infertility. A less common phenotype in a mild form of androgen receptor dysfunction leads to normal fertility but mild reduction in body hair (Grino et al. 1988).

7.9.1 Management

Assessment of androgen insensitivity syndrome involves hormone profile, sequencing of the AR gene, imaging to locate the testes and for cancer surveillance, and possible trial of testosterone ester administration. Androgen receptor binding studies in cultured fibroblasts from genital skin biopsy is performed in research settings, and a sex-hormone binding-globulin androgen sensitivity test has been proposed, but is not widely used in clinical practice. Testosterone levels are usually normal or high in infancy, from puberty, or with testicular hCG stimulation. Luteinising hormone and sex hormone binding globulin levels are often elevated.

A large number of mutations in the androgen receptor gene (AR) have been reported, with coding region mutations found in nearly all CAIS patients but only 20% of PAIS patients (Deeb et al. 2005). The AR mutation is inherited in an X-linked manner, and a single mutation can have variable penetrance in phenotype.

Testis location can be assisted by ultrasonography or MRI if clinical examination is negative. Clinical trial of testosterone administration in infancy, using 25 mg testosterone esters monthly for 3 months, can provide an indication of genital virilisation potential if there is an increase in phallus size.

In individuals with partial androgen insensitivity syndrome, the androgen resistance may be overcome by administration of supra-physiological testosterone doses. Long-term risks of this therapy are unknown, however adverse outcomes have not yet been reported.

Gynaecomastia is associated with testosterone aromatisation and can be treated with mastectomy if troublesome. Infertility can be treated with assisted reproduction technology, using the individual's own gametes if viable, or donor gametes. Germ-cell cancer should be managed according to the risk stratification by regular examination and annual imaging and tumour-marker analysis from puberty, or risk-reducing gonadectomy.

Gender assignment decisions are straightforward for individuals with complete or near complete androgen

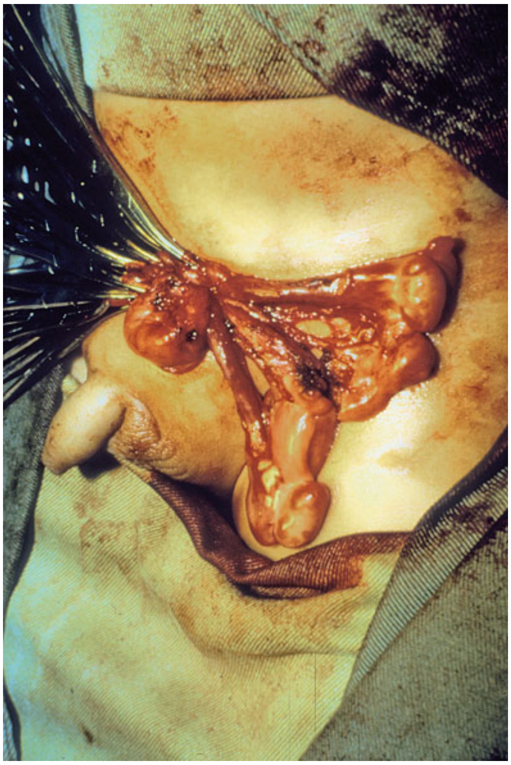

Fig. 7.6 Boy presenting with undescended testes and inguinal hernia, found at operation to have persistent Müllerian duct syndrome (PMDS). The hernia sac contains a loop of bowel as well as 2 testes and spermatic cords, as well as oedematous Fallopian tubes and a small uterus

insensitivity, or mild partial androgen insensitivity. However in more significant grades of partial androgen insensitivity where virilisation is equivalent to Prader stage 2, gender assignment can be difficult as there may be a limited potential for future virilisation. Optimal management, regardless of sex of rearing, would allow preservation of future options for anatomically congruent gender identity, i.e. not removing erectile tissue from the phallus. In this group, rigorous consideration of ethical principles should accompany decision-making.

7.10 Persistent Müllerian Duct Syndrome

Mutations in the gene encoding Müllerian inhibiting substance/anti-Müllerian hormone (MIS/AMH) or its receptor will lead to persistence of Müllerian duct organs in a 46,XY individual (Fig.7.6). These are inherited in an autosomal recessive manner. The usual presentation is of a phenotypic male with cryptorchidism, and the uterine remnant may become apparent only with thorough investigation in the newborn period, or later with inguinal herniation of Müllerian tissue or incidentally at laparoscopy for other reasons (Colacurci et al. 1997; Hutson et al. 1987; Hutson et al. 1997).

Management involves surgical resection of the Müllerian structures and repair of any cryptorchidism with usual follow-up for a history of undescended testes.

7.11 DSD Due to Non-Hormonal Anatomical Defects

Defects in urogenital and lower abdominal anatomical development cause disorders of sex development through androgen-independent mechanisms. These disorders include the spectrum of epispadias, bladder and cloacal exstrophy, and disorders of cell proliferation and development as found in other more pleiotropic syndromes (see Chap. 9).

Epispadias represents urethral opening on the dorsal aspect of the penis, estimated to occur in 2.4 per 100,000 male births (International Clearinghouse for Birth Defects Monitoring Systems 1987). It is understood that most patients with epispadias also have the more severe bladder exstrophy, where a defect in lower abdominal wall closure leads to a bladder with the inner surface exposed. Bladder exstrophy occurs in 3.3 per 100,000 live births. Cloacal exstrophy is characterised by both bladder and gut exstrophy, and occurs with an incidence of 0.5 per 100,000 live births.

The cause of the lower abdominal wall defect has not yet been delineated, and it is thought that there are anatomical factors impeding migration of the mesenchymal tissue toward the midline. A defect in factors driving tissue migration would be another possible mechanism. Candidate genes involved in midline urological development include P63 (Cheng et al. 2006; Qi et al. 2011).

Surgical repair of anatomical defects that involve the genitalia aims to restore urogenital and gut function along with improvement of appearance. Multiple surgical procedures are often required. Long-term medical issues relate to continence, renal impairment and reduced fertility, with retrograde ejaculation reported (Ebert et al. 2008). Dissatisfaction with genital and body appearance is common, with only 60% of post-pubertal males reporting satisfactory intercourse (Mesrobian et al. 1986).

Disorders in tyrosine kinase receptors (Robinow Syndrome), cell proliferation (Opitz G syndrome), homeobox gene function (Hand-foot-genital syndrome) and midline organogenesis (CHARGE syndrome) can also lead to abnormal morphogenesis of the genitalia.

Congenital bilateral aplasia of the vas deferens can occur sporadically, but also occurs in 95% of patients who have cystic fibrosis (Rey and Grinspon 2011).

7.12 Conclusion

Whilst 46,XY DSD comprise a heterogeneous group of disorders with varying natural history and complication risk stratifications, and an accurate diagnosis is not afforded to many individuals. There is a clinical responsibility to provide an accurate diagnosis if possible, to provide appropriate medical care. In concert with this is an obligation to pursue research which improves diagnostics, and further illuminates the long-term diagnosis-specific risks and optimal medical management and counselling.

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Mixed Sex Chromosome and Ovo-Testicular DSD

8

Jacqueline K. Hewitt and Garry L. Warne

8.1 Mixed Sex Chromosome DSD

Mixed sex chromosome DSD occurs where there is sex chromosome aneuploidy - an abnormality in the number of X or Y chromosomes, with the addition or loss of an entire chromosome. It is extremely common, with an incidence of 1:400 births. In some individuals it may affect all cells. The most common aneuploid karyotypes found are 47,XXX (1:947 girls), 47,XXY (1:576 boys), 45,X (1:1893 girls) and 47,XYY (1:851 boys) (Nielsen 1991). Alternatively, the aneuploidy may form part of a mosaic karyotype. The most common of these found are 45,X/46,XX, 45,X/46,XY, 46,XX/47,XXX, and 46,XY/47,XXY. The definition of DSD (congenital conditions in which chromosomal, gonadal or anatomical sex is atypical) includes sex chromosome aneuploidy and sex chromosome mosaicism. In many conditions associated with sex chromosome aneuploidy or mosaicism, the development of the gonad is adversely affected, and therefore puberty and fertility, even primary sex differentiation, may be impaired. This is not the case, however, for two types of sex chromosome aneuploidy. In 47,XYY and 47,XXX syndromes, sex differentiation, puberty and fertility are normal, and they are not discussed in detail, except in Chap. 20, on genetic counselling.

In the past, some unwarranted assumptions were made about the phenotype of individuals with sex chromosome aneuploidy and mosaicism. A different picture emerged from long-term follow-up of individuals detected through cytogenetic surveys of the newborn that were begun in collaboration between a number of centres in North America and Europe in the 1960s. Out of 199,898 consecutive newborn live births screened by examination of amniotic membranes, buccal smear or cord blood, 307 individuals were identified and invited to participate in follow-up studies, along with age- and sex-matched controls. The results show that "most of these individuals with sex chromosome aneuploidy fall within the normal range in development and that marked abnormality is not usually seen" (Linden et al. 1996). Further unbiased information emerged from follow-up studies of infants born following intra-uterine diagnosis. A surprising finding was that 95% of infants with prenatally diagnosed 45,X/46,XY mosaicism had a normal male phenotype, rather than the ambiguous genitalia that clinicians were more used to seeing in patients diagnosed after birth (Chang et al. 1990).

8.2 45,X/46,XY Mosaicism

This is the commonest chromosomal abnormality associated with ambiguous genitalia and, together with congenital adrenal hyperplasia (CAH) and androgen insensitivity syndrome, one of the three most common known causes of ambiguous genitalia overall. The

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abnormal anatomy in 45,X/46,XY mosaicism results from gonadal dysgenesis. When one gonad is a streak (consisting of fibrous tissue without any germ cells) and the other is a dysgenetic testis, the patient is said to have *mixed* gonadal dysgenesis. When both testes are dysgenetic, the term used is *partial* gonadal dysgenesis. The histological characteristic of testicular dysgenesis is a cortical network of anastomosing seminiferous cords that penetrate a thin tunica albuginea. In streak gonads, the 45,X cell line predominates over the 46,XY line, while in dysgenetic testes, the two cell lines are more equally balanced (Chemes et al. 2003).

8.2.1 Cancer Risk and Risk Management

Histological features of dysgenetic testes may also include two pre-malignant types of germ cell: gonadoblastoma and carcinoma-*in-situ* (Looijenga et al. 2007). The features of a gonadoblastoma are germ cell proliferation and sex cord derivatives frequently surrounding small round deposits containing amorphous hyaline material (Gorosito et al. 2010). Gonadoblastomas are found more commonly in undifferentiated gonads. Gonadoblastomas may be bilateral and may be present from birth, or they may develop later. All are thought to have the potential to transform into malignant seminomas/dysgerminomas over time. Carcinoma-*in-situ* cells are found lining seminiferous tubules in dysgenetic testes. They resemble immature germ cells and cannot therefore be diagnosed early in life, when such cells are normally present, but if found in the testes of an older boy, they are pathological and are capable of transforming into seminomas. Expression of two genetic markers – *OCT3/4* and *TSPY* – in the intratubular germ cells of an older boy is regarded as pathognomonic of CIS (Looijenga et al. 2010). The risk of gonadal cancer in an individual with severe gonadal dysgenesis and 45,X/46,XY mosaicism is high, especially if the gonad is intra-abdominal, when the risk is approximately 50% (Hughes et al. 2006; see Table 22.3). The risk in a better differentiated, scrotal testis is somewhat lower but still too high to be ignored. Risk management strategies need to take these facts into account. Intra-abdominal dysgenetic testes and streak gonads *must be removed as soon as possible after diagnosis*. Earlier advice would have been also to remove the better differentiated scrotal or inguinal testis, given the overwhelming likelihood of infertility, the high chance of hormonal deficiency needing replacement therapy and the risk of cancer, but the removal of gonadal tissue in patients with DSD has more recently become a subject of considerable controversy, requiring court authorization in some countries (Warne and Mann 2011). If a dysgenetic testis is to be retained, a risk management strategy is mandatory. This would include bringing an inguinal testis down to the scrotum for examination purposes, regular clinical follow-up and biopsy after the onset of puberty, with specialized pathological examination (including staining for *OCT3/4* and *TSPY*), to exclude CIS. If evidence of CIS is found, the testis can be either removed or irradiated (Skakkebaek 1994). The reason for waiting until after the onset of puberty is that by that time, CIS cells would have spread to involve more of the seminiferous tubules and sampling error would be low. As previously stated, it would be inappropriate to perform the biopsy in a young boy, when it would be impossible to differentiate CIS cells from immature germ cells.

8.2.2 Phenotype of 45,X/46,XY DSD

A wide range of phenotypes is possible with this karyotype. At one end of the spectrum, representing 95% of the total number of affected individuals, are those with an apparently normal male phenotype. Follow-up of these boys has shown that many have short stature and dysgenetic testes (Telvi et al. 1999). The risk of gonadal cancer in this group is unknown but is likely to exceed that of the normal male population.

At the other end of the spectrum are those with a female phenotype and features of Turner syndrome. Estimates of the number of girls with Turner syndrome whose karyotype contains Y chromosome material vary, depending on the detection technique used (Nishi et al. 2002; Yorifuji et al. 2001; Hanson et al. 2001), and the ideal method of screening for this has not been clearly defined. The incidence of gonadoblastoma in women with 45,X Turner syndrome is low, but it is significantly higher in those with all or part of a Y chromosome. The presence of *TSPY* has been postulated to be the best indicator of cancer risk (Hersmus et al. 2008). A high frequency (47%) of Y chromosome deletions has been identified in patients with sex chromosome mosaicism and these are believed to contribute to Y chromosome instability (Patsalis et al. 2005).

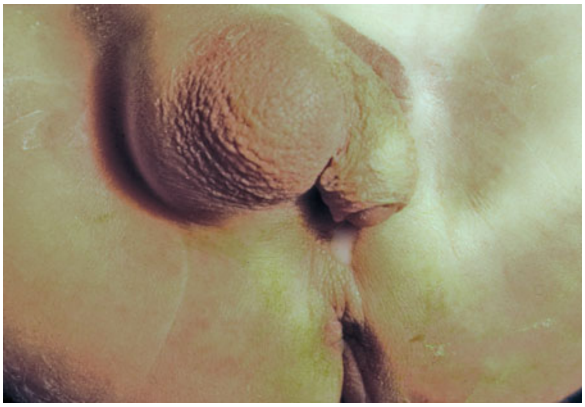

Fig. 8.1 In 45,X/46,XY mixed gonadal dysgenesis the gonadal mosaicism leads to asymmetrical external genital development. In this patient, the right gonad was a reasonable testis that had descended into the hemi-scrotum, while on the left side the gonad was an intra-abdominal streak gonad, producing striking genital asymmetry. A vaginal cavity was present inside the common urogenital opening, as can be predicted from the presence of vaginal mucus below the phallus (stimulated by maternal hormones). He was raised as a boy, with the gonads left in situ. He re-presented in adolescence with a tumour arising from the streak gonad

Infants with mixed gonadal dysgenesis typically have ambiguous genitalia that have an asymmetrical appearance, due to the presence of a descended testis on one side and an impalpable, intra-abdominal streak on the other (Fig. 8.1). The better differentiated testis is usually smaller than a normal testis. Around 75% have a uterus, due to insufficient foetal testicular secretion of Mullerian inhibitory substance (MIS/AMH), but the uterus may be a hemi-uterus or otherwise incompletely formed and the risk of endometrial cancer is thought to be increased (Robboy et al. 1982). Either a large utricle or a vaginal remnant may be present and this may predispose to recurrent urinary tract infection if there is backfilling with urine. Short stature is found in 84% and growth hormone treatment would usually be offered (Lara Orejas et al. 2008). Abnormalities of the urinary tract (axial rotation of the kidney, ureteric duplication, horseshoe kidney, renal dysplasia) and cardiovascular system (arterial hypertension, coarctation of the aorta, bicuspid aortic valve) may be present (Telvi et al. 1999). Some patients have learning difficulties, an increased risk of deafness due to recurrent otitis media, and dysmorphic features resembling those of Turner syndrome.

8.2.3 Management

As discussed above, a risk management strategy to prevent death from cancer is most important in all patients with sex chromosome mosaicism including a Y chromosome or a marker derived from the Y chromosome. Streak gonads can be removed laparoscopically. The decision as to the removal or retention of a dysgenetic testis will depend upon several factors: the sex of rearing, the perceived cancer risk, the likelihood that the testis will secrete enough testosterone for normal pubertal development and the possibility of fertility. Ethically, an important aim should be to minimize physical harm to the child (Gillam et al. 2010) and the elimination of cancer risk would justify removing the gonad. Maximizing the potential for fertility would mitigate against removing it, but if a biopsy showed a complete absence of germ cells, there would be no chance of fertility (in the future, germ cell transplantation or stem cell therapy may offer a solution) and therefore the gonad could be removed. Hormonal function is often inadequate for normal puberty in dysgenetic testes, making hormone replacement therapy necessary in most cases, so this is not a reason for retaining a dysgenetic testis.

The decision about the sex of rearing has "traditionally" been closely related to the degree of masculinisation, or lack of it, in the external genitalia (Cameron et al. 1997) but the gender identity of the individual cannot reliably be predicted from the genital anatomy (Warne 2008). While in the majority of cases, the affirmed gender identity will match the sex assigned at birth, a significant number will experience severe gender dysphoria on reaching puberty, especially if they were raised female and had feminising genitoplasty (Szarras-Czapnik et al. 2007) and some will demand further surgery to change their anatomical sex. This is an outcome to be avoided at all costs if possible, and therefore the key ethical considerations should be to keep future options open (meaning that feminising genitoplasty should be avoided in patients whose future gender identity may be male) and to maximize the potential for satisfying sexual relations, which in this case means not removing genital tissues that might be wanted later on. The wishes and beliefs of the parents will also come in to the decision-making process. Where strong preferences are expressed for cultural reasons (Warne and Raza 2008), they will often favour a male sex of rearing.

Long-term management will include hormone replacement therapy (Warne et al. 2005b), with oestrogen for those whose gonads were removed and who were raised female (combined with a progestogen when a uterus is present), and testosterone for male patients. Referral of female patients to an adolescent gynaecologist at pubertal induction allows counselling about physical development, gender identity and relationships, and consideration of the need for further surgery to widen the introitus prior to menstruation and sexual debut (see Chap. 23). The involvement of an experienced mental health professional is also strongly recommended (see Chap. 24).

Patients who have had hypospadias surgery and who have been raised male are usually in the care of a paediatric urologist and an endocrinologist (for both growth hormone therapy and sex hormone replacement). Long-term follow-up studies have revealed a high incidence (44%) of persisting urinary difficulties (Warne et al. 2005a). Boys may be troubled by unstable gender identity and uncertainty about sexual orientation as they reach puberty and they may also have poor self esteem because of their small penis. Typically, the penis in boys who have had severe hypospadias is short and broad. Long-term outcome studies of adolescents who were born with either ambiguous genitalia or micropenis show that they experience a range of difficulties,(de Vries et al. 2007; Brinkmann et al. 2007) however the current services caring for these boys and men include little provision in terms of professional mental health support.

8.3 Ovo-Testicular DSD

In ovo-testicular DSD, ovarian follicles and seminiferous tubules are present in the gonads of the one individual. Their distribution in the gonads varies. One pole of a gonad may consist of ovarian tissue, while the other pole consists of testicular tissue. Another variation is that one gonad is an ovary while the other is a dysgenetic testis. In 89% of ovotestes, however, the ovarian and testicular elements are evenly distributed throughout, making it impossible to distinguish one from the other at the macroscopic level (Fig. 8.2; Wiersma and Ramdial 2009).

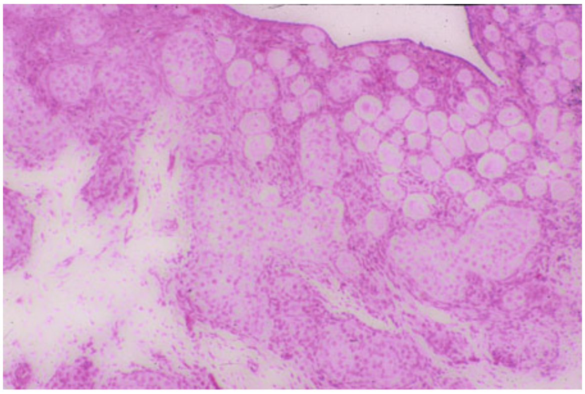

Fig. 8.2 Gonadal histology in a baby with ovo-testicular DSD. The section shows relatively normal seminiferous tubules alongside ovarian stroma with follicles

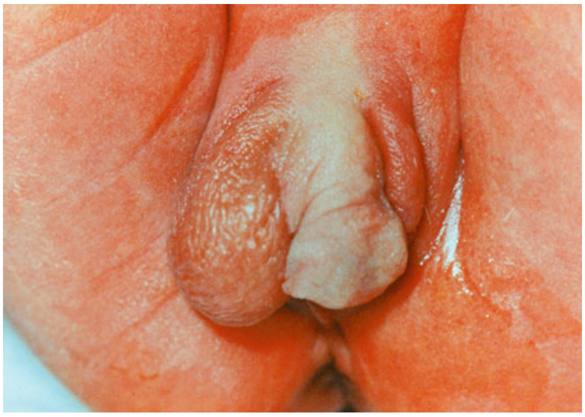

Fig. 8.3 Ovo-testicular DSD in a baby with external asymmetry. On the right the descended gonad was a testis, while the undescended left gonad was an ovo-testis

The testicular tissue in ovo-testicular DSD undergoes atresia at a faster rate than the ovarian tissue; while a small number of women with ovo-testicular DSD have become mothers, paternity has never been reported.

The karyotype in ovo-testicular DSD is most commonly 46,XX (96.9% of cases reported in Africa), but 45,X/46,XY and 46,XY ovo-testicular DSD are seen (Krob et al. 1994). Occasionally 46,XX/46,XY chimeras are also seen. The cancer risk in ovo-testicular DSD with a 46,XX karyotype is classified as low (Looijenga et al. 2010), but the risk in patients with a Y chromosome is assumed to be higher.

The phenotype varies, depending on the gonadal status, but one easily recognisable pattern is when there is a testis on one side (often the right) and an ovo-testis or ovary on the other side (Fig. 8.3).

8.3.1 Management of Ovo-Testicular DSD

The gonad most likely to function in an individual with ovo-testicular DSD is the ovary. The uterus may be normal, hypoplastic or absent (Yordam et al. 2001). Of 36 Brazilian patients with ovo-testicular DSD, the female option was taken in 55.6% (Damiani et al. 2005). Given that the gonadal cancer risk in 46,XX ovo-testicular DSD is low, that fertile oocytes may be present in the ovarian tissue but spermatogenesis is always absent, it is recommended that the testicular component be excised if it can be identified (Wiersma 2001). If not, it may be an option to leave the ovo-testis in situ, review the hormonal status at puberty and remove tissue that is producing unwanted hormones (which may involve excision of the whole gonad).

8.4 Klinefelter Syndrome – 47,XXY

Genital anomalies are seen only rarely in males with a 47,XXY karyotype (Lee et al. 2007), although progressive deterioration of testicular function is a feature in the majority of patients (Wikstrom and Dunkel 2008) and testosterone replacement therapy is required for many men (Forti et al. 2010). One of the benefits of testosterone therapy is the prevention of osteoporosis, which is present in 40% of men with Klinefelter syndrome (KS) (Ferlin et al. 2010). Most men with KS are oligospermic or azoospermic, with high levels of FSH and LH but some success has been reported with assisted reproductive technologies, particularly intra-cytoplasmic sperm injection (ICSI) (Paduch et al. 2009). Males with KS tend to be taller than average. In intelligence they fall within the normal range but there is a deficit of 10–15 IQ points in comparison with siblings (Linden et al. 1996). Verbal IQ is affected more than performance IQ. At puberty, gynaecomastia occurs in one-third of boys and this may require surgical treatment. There is an increased life-time risk of breast cancer. Men with KS are also at increased risk of non-testicular germ cell cancers, especially in the mediastinum (Hiramatsu et al. 2008).

8.5 Turner Syndrome – Monosomy X

Loss of one of the two X chromosomes (either the maternal X or the paternal one) results in a wide range of changes in foetal development. All except 1% of 45,X foetuses are spontaneously aborted (Linden et al. 1996).

The phenotypes of live-born girls with TS vary markedly, but may include abnormalities in linear growth (average adult height is 144 cm), ovarian differentiation, development of the cardiovascular, lymphatic and renal systems, the eyes and ears and other organs (Sybert 1984). Infants may be born with webbing of the neck, which in foetal life was actually a lymphatic malformation, commonly called a cystic hygroma. This abnormality, in turn, results from obstruction to the thoracic duct. Other lymphatic abnormalities are responsible for the development of lymphoedema of the hands and feet, which can be troublesome. Typical cardiovascular anomalies are bicuspid aortic valve and coarctation of the aorta. Essential hypertension is a risk during adolescence and adulthood. Girls with TS are prone to obstruction of their Eustachian tubes and are therefore prone to otitis media, conductive deafness and cholesteatoma. In addition, nerve deafness, which is independent of the conductive deafness, tends to develop towards the end of the second decade and by middle age more than a quarter of women with TS require a hearing aid (Bergamaschi et al. 2008; Morimoto et al. 2006; Beckman et al. 2004; Hultcrantz et al. 1994). Other head and neck abnormalities include high-arched palate, downturned angles of the mouth, strabismus and epicanthic folds. There is often an increased number of pigmented cutaneous naevi and wound healing is often with keloid scarring.

There are some psychological characteristics that may affect learning, even though mean IQ is within the normal range for the general community. Individual IQ in comparison to that of siblings is reduced by an average of 24 points (Mazzocco 1998). A number of Wechsler scores (particularly Arithmetic, Block Design, Object Assembly and Picture Arrangement) are negatively affected in TS females as a group (Loesch et al. 2005).

In the long-term, the main issues that affect quality of life for women with TS are short stature, infertility and deafness, in addition to increased risk for the metabolic syndrome, autoimmune diseases (hypothyroidism and coeliac disease) and osteoporosis. A particular mortality concern is the risk of dilatation of the aortic root. This occurs most commonly in women with bicuspid aortic valve but can also occur in those without previously detectable cardiac anomalies. Sudden death may occur in early adult life due to dissecting aneurysm and strategies aimed at preventing it have been proposed (Conway

2009). Women with TS who have premature ovarian failure are very interested in assisted reproductive technologies (Huang et al. 2008; Cabanes et al. 2010) and a number of pregnancies have resulted from IVF, but the maternal risks are considerable. Foetal outcomes are also relatively poor with regard to risk for spontaneous abortion and chromosomal anomalies in the infant (Mortensen et al. 2010; Georgopoulos et al. 2009).

8.5.1 Detecting Mosaicism in Patients with TS

Around 30% of individuals with TS have sex chromosome mosaicism. Those with 45,X/46,XX mosaicism have a better chance of fertility than those with 45,X and there is speculation that cryopreservation of ovarian tissue before all of the oocytes have undergone atresia may improve homologous reproductive chances (Huang et al. 2008). Some TS patients have 45,X/46,XY mosaicism and because of the Y chromosome, are at increased risk for germ-cell cancer (Looijenga et al. 2010). Once they have this diagnosis, the streak gonads should be removed (Cools et al. 2006). The difficulty lies in detecting low levels of mosaicism. At least 100 cells need to be counted to exclude low-level mosaicism in those who appear to have a 45,X karyotype (Wolff et al. 2010). Quantitative PCR is also able to detect very small amounts of Y-derived DNA but can have a high false positive rate. An alternative strategy that has been proposed (Dr H Slater, personal communication) would be to identify the parental origin of the chromosome that was lost. This can be done by examining epigenetic markers. If the retained chromosome is of *paternal* origin, then the missing chromosome cannot be a Y chromosome and there should be no need to screen for Y material. This would reduce the workload by approximately 40–50%. The current recommendation, however, is for fluorescent-in-situ-hybridisation for X and Y centromere probes to be performed on a minimum of 200 interphase cells in girls with a 45,X karyotype (Wolff 2010).

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Non-hormonal DSD

9

John M. Hutson

9.1 Introduction

Abnormalities of genital development that lead to DSD are usually secondary to defects in gonadal or hormonal function, but there is also a large group of congenital malformations affecting the abdominal wall and perineum that also lead to genital deformity. These disorders can be classified into those where the internal or external genitalia are abnormal because of abnormal morphogenesis of the genital tract alone, or where the genital anomaly is part of a more widespread abdominal or perineal deformity (Table 9.1) (Stephens et al. 2002).

The key to recognition of these anomalies is that the external anatomy is outside the range between normal male through to normal female. In particular, there is an anatomical defect that is beyond the normal effects of androgens acting on the genital tubercle and genital folds. By contrast, in hormonal causes of DSD, the morphological development is otherwise normal, and the dysmorphology is merely a consequence of abnormal androgenic or MIS/AMH function.

Table 9.1 Classification of non-hormonal DSD

Site of dysmorphogenesis	Disorder
Internal genital ducts	Urogenital ridge or gonadal duplication/agenesis Müllerian duct malunion Vaginal duplication/agenesis Rokitansky sequence (MRKHS)
External genitalia	Penile agenesis Ectopic labium/scrotum Urogenital sinus
Lower abdominal wall	Bladder exstrophy Epispadias
Perineum	Anorectal malformations Cutaneous fistula Rectobulbar fistula Acquired anomalies secondary to embryonic/foetal compression
Cloacal development	Partial twinning Cloacal anomaly Cloacal exstrophy Caudal regression

9.2 Internal Genitalia

The commonest anomaly of the internal genital development is failure of normal fusion of the Müllerian ducts, leading to various degrees of uterine and vaginal separation. There may be a completely duplicated genital tract right through to a partial bicornuate uterus. Complete duplication may be obvious on inspection of the introitus, while most other anomalies are only documented at endoscopy or laparoscopy, or on imaging studies (Fig. 9.1).

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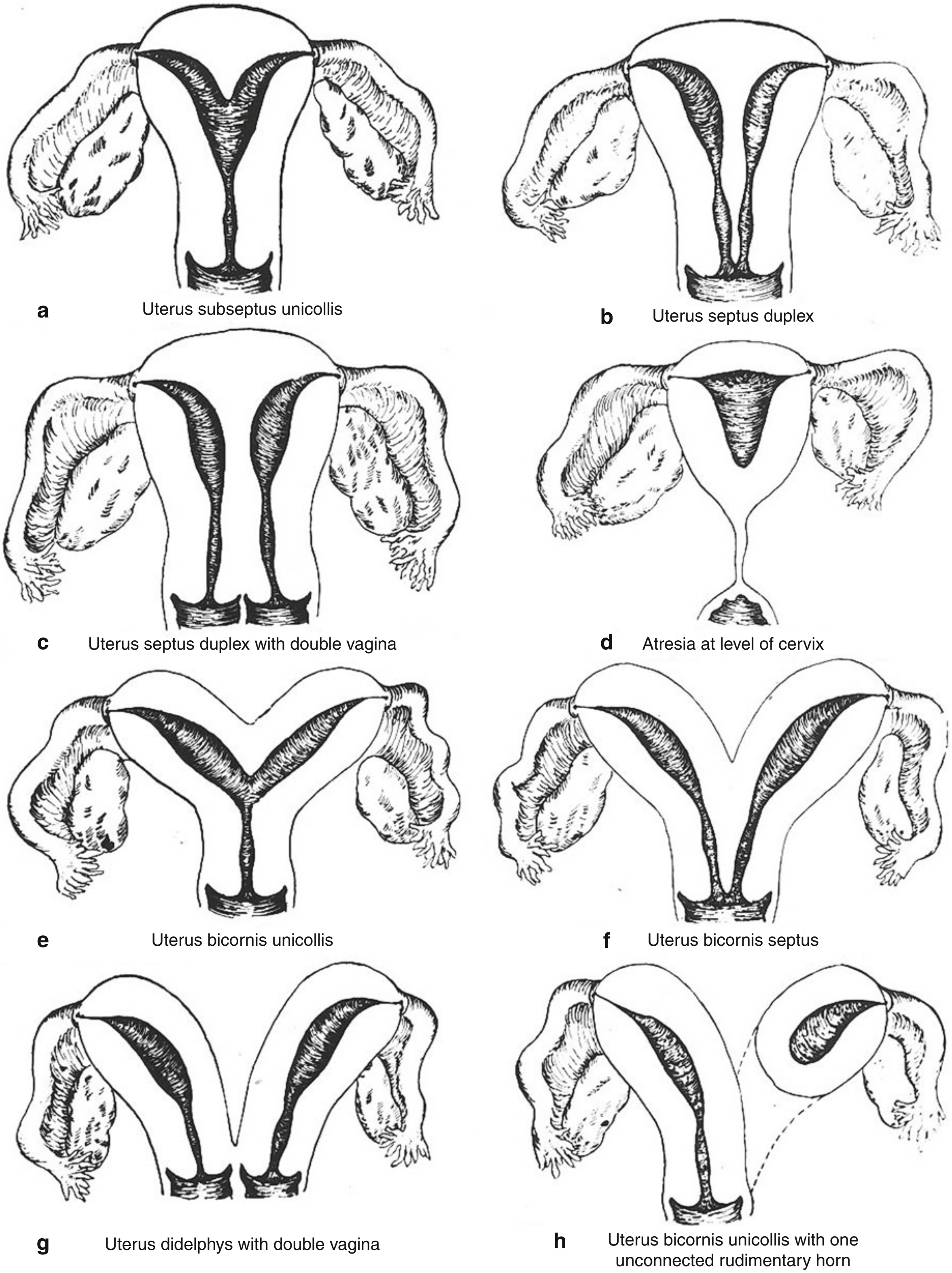

a Uterus subseptus unicollis

b Uterus septus duplex

c Uterus septus duplex with double vagina

d Atresia at level of cervix

e Uterus bicornis unicollis

f Uterus bicornis septus

g Uterus didelphys with double vagina

h Uterus bicornis unicollis with one unconnected rudimentary horn

Fig. 9.1 Schematic diagrams of abnormal fusion of the paired Müllerian ducts and types of atresia (Reproduced with permission from Stephens et al. 2002)

Box 9.1: Mayer-Rokitansky-Küster-Hauser (MRKH) Syndrome

MRKH syndrome (OMIM 277000) with agenesis of part of all of the female genital tract is present in about one in 400–500 females. It can be classified into two subgroups; those with or with associated anomalies.

MRKHS Type I (OMIM 277000): Isolated Müllerian duct agenesis with absent uterus and vagina.

MRKHS Type 11 (OMIM 601076): Müllerian duct agenesis with associated abnormalities of the urogenital ridge (Wolffian duct development, ureteric bud development, renal dysplasia) and cervical somites (also called MURCS association. Müllerian duct agenesis, Renal anomalies, Cervical Somite anomalies). This may also be called GRES (Genital Renal Ear Syndrome; OMIM 267400) when there are abnormalities of the middle ear, with associated deafness (Morcel et al. 2007; Bernardini et al. 2009).

Complete or partial duplication in the urogenital ridge is well described, and this may present as an extra testis.

Agenesis of the female genital tract is a serious DSD, with important implications for the woman in both function and psychological development (Box 9.1). One of the key causes for Müllerian duct agenesis is a primary abnormality in the mesonephros and its duct, the mesonephric or Wolffian duct. The latter is an intrinsic organiser of Müllerian development, as the Müllerian ducts use the Wolffian ducts to guide their migration to the cloaca between 6 and 8 weeks of gestation. The elongating solid tips of the Müllerian ducts grow along the basement membrane of the adjacent Wolffian ducts. Failure of the Wolffian duct to reach the cloaca by 4 weeks of gestation may prevent the ureter budding from the lower Wolffian duct (leading to ipsilateral renal agenesis), as well as distal agenesis of the Müllerian duct (Rokitansky sequence). This is the classic anomaly of the MRKH syndrome type II (Stephens et al. 2002). When the abnormality occurs later, for example, between 8 and 12 weeks of development, the vagina may fail to canalise, leading to atresia, but the urinary tract is not affected, and would lead to MRKH syndrome type 1 (see Fig. 2.7; Table 9.2).

Table 9.2 Timing of events in urogenital tract

Weeks	Crown–rump length (mm)	Urinary tract	Genital tract
4	5	Wolffian duct reaches cloaca Ureteric bud forms	
5	8	Ureter + pelvis form kidney "ascending"	
6	12	Ureter separates from Wolffian duct	MD forms
7	17	Urogenital membrane ruptures	
8			MDs reach cloaca
10	40	Kidneys make urine	WD regressing in female
12	55–65	Ureteric orifice in bladder	Uterus canalising vaginal plate migrating
20	150		Vaginal lumen hymen ruptures

From Stephens et al. (2002)

9.3 External Genitalia

Isolated anomalies of the external genitalia may be readily confused with hormonal causes of DSD, but the over-riding feature is that the anatomy is aberrant, and cannot be explained by abnormal hormonal effects. Failure of the genital folds to form around the cloacal membrane is a sign of an early anomaly of fundamental embryogenesis, and hence is relatively uncommon in surviving babies. Such defects include ectopia of the outer genital fold, leading to ectopic hemiscrotum or labium majora (Fig. 9.2). More fundamental defects may include complete absence of the genital tubercle to form, which causes penile agenesis in boys. In this rare anomaly the urethra usually opens via an abnormally located meatus within the anterior lip of the anal canal, if present. An important clue to the prognosis is the presence of a median raphe in the scrotum; when this is absent there is a very high likelihood of renal dysplasia or agenesis (Fig. 9.3) (Srinivasan et al. 2003).

Where the vaginal plate forms but there is defective caudal elongation and migration to the vestibule, the baby girl is born with a common opening for the urinary and genital tracts, known as a urogenital sinus. This is not related to androgenic suppression of vaginal plate development, as the vagina is otherwise well

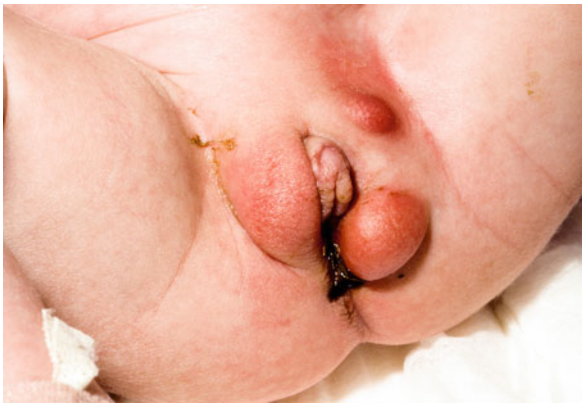

Fig. 9.2 Ectopic labium majora, secondary to failure of the outer genital fold to develop around the cloacal membrane, in a baby with a recto-vestibular fistula

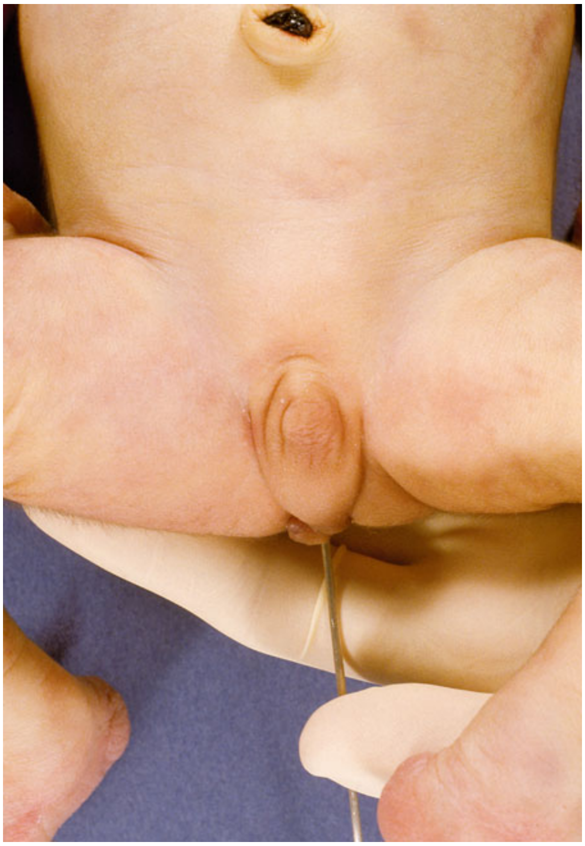

Fig. 9.3 Penile agenesis, showing empty scrotum which has no median raphe. The baby had cystic dysplasia of ectopic pelvic kidneys (Reproduced from Srinvasan et al. 2003 with permission of the publisher)

formed; the defect lies in the genetic regulation of migration of Müllerian tubercle and vaginal plate to the vestibule. Acquired adhesion of the labia minora is occasionally misdiagnosed as a congenital anomaly. However, this is secondary to vulvovaginitis with ulceration of the labia minora and accidental adherence during healing. Ammonia dermatitis is the usual cause. Labial adhesions are rarely noticed below 6 months of age, and frequently present from 6 months up to 2–3 years, when girls become toilet trained (Leung et al. 1993).

9.4 Lower Abdominal Wall Defects

The lower anterior abdominal wall is formed by ectoderm during embryonic folding, as well as by migration of lateral plate mesoderm around the developing trunk to form the muscles of the abdominal wall. Migration of mesodermal cells between the umbilical stalk and the immediately adjacent cloacal membrane leads to proliferation of muscle precursors that will form the abdominal wall musculature as well as contribute to the development of the anterior bladder wall. Failure of the mesenchymal expansion may lead to various defects in the lower anterior abdominal wall, from classic bladder exstrophy through to epispadias. The anatomy in classic bladder exstrophy, where the genital tubercle in males is often separated from the outer genital folds (that form the scrotum) by a bridge of skin, suggests that the mesenchyme may have migrated aberrantly between the genital tubercle and the outer genital folds, disrupting the urethral development and leaving a deficiency in the abdominal wall above the genital tubercle (Fig. 9.4a).

Epispadias is a less severe variant where confusion with other DSD is less likely, although in girls the clitoris may be bifid (Fig. 9.4b), while in boys the urethra and penis are abnormal (Fig. 9.4c).

9.5 Perineal Anomalies

Perineal development includes not only the urogenital tracts, but also the hindgut, so that anomalous development may affect all three tracts and their respective

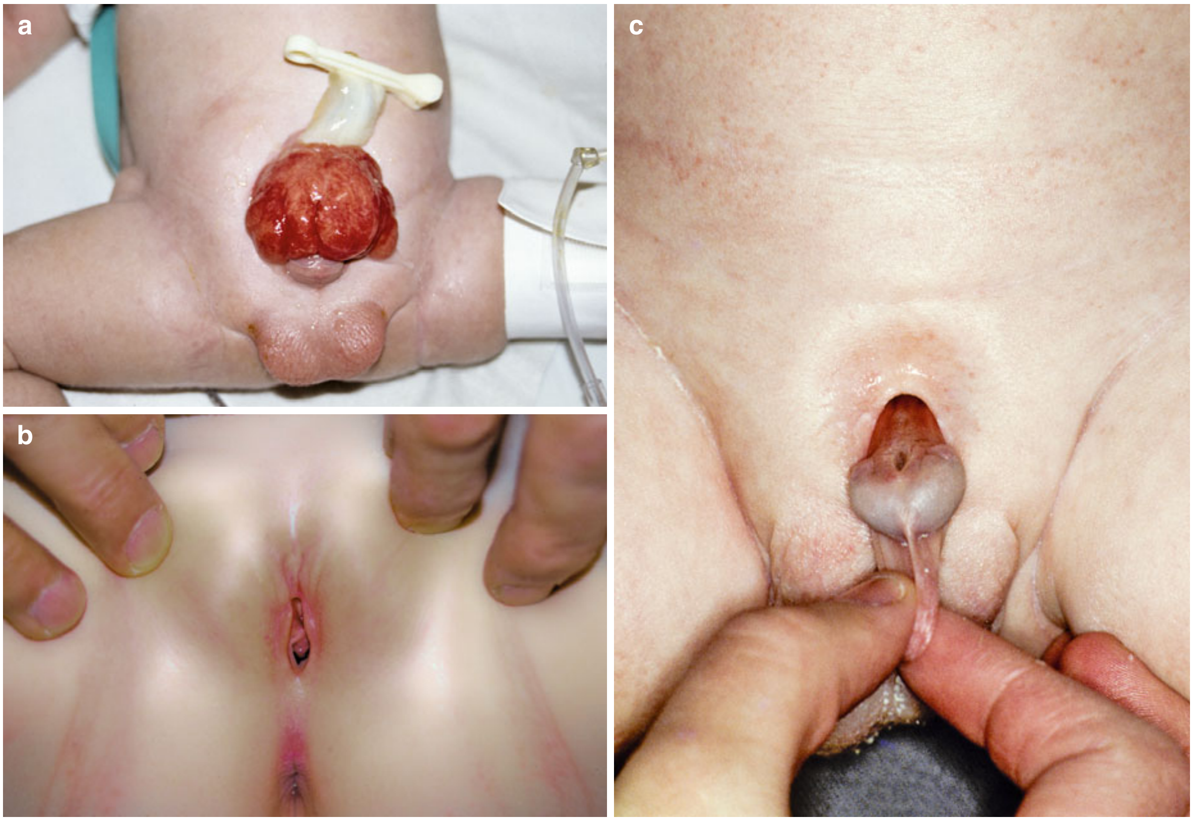

Fig. 9.4 (**a**) Classic bladder exstrophy, with deficiency of the anterior abdominal wall and the anterior wall of the bladder and urethra. Note the skin bridge between penis and scrotum. (**b**) Epispadias in a girl showing a bifid clitoris. (**c**) Epispadias in a boy showing the open urethral plate exposed on the dorsal surface of the penis

external openings (Holschneider and Hutson 2006). One characteristic anomaly in this category is an anorectal malformation with a cutaneous fistula, which usually is within the median raphe in the male. The anatomy in boys with a rectobulbar urethral fistula is potentially ambiguous, as the abnormal connection between the terminal hindgut and the bulb of the urethra is often associated with nonfusion of the hemiscrotal folds (Fig. 9.5a).

In females with anorectal malformations the fistula is most commonly in the vestibule, leading to variable degrees of dysmorphogenesis of the external genitalia. The absence of an obvious anal opening, however, is a clear sign of a non-hormonal anomaly of embryogenesis (Fig. 9.5b).

In some foetuses, the genital anomaly is secondary to compression of the foetus in utero, with pressure atrophy of variable genital and perineal structures. In a recent case, the boy presented with chordee of the penis associated with not only deficient ventral growth of the penile shaft, but also an abnormal urogenital opening. In addition, the left hemiscrotum was hypoplastic and the testis was absent. Initially the boy was thought to have mixed gonadal dysgenesis or ovo-testicular DSD, but careful inspection of the external genitalia revealed that the urethral meatus was on the tip of the glans at the normal site. The opening on the ventral surface looked like a pressure sore or a urethral fistula after hypospadias repair, rather than a urogenital sinus. Careful palpation revealed an atrophic nubbin in the left hemiscrotum consistent with ischaemic atrophy. At examination under anaesthesia it was possible to show that the right heel of the boy fitted perfectly into the perineum,

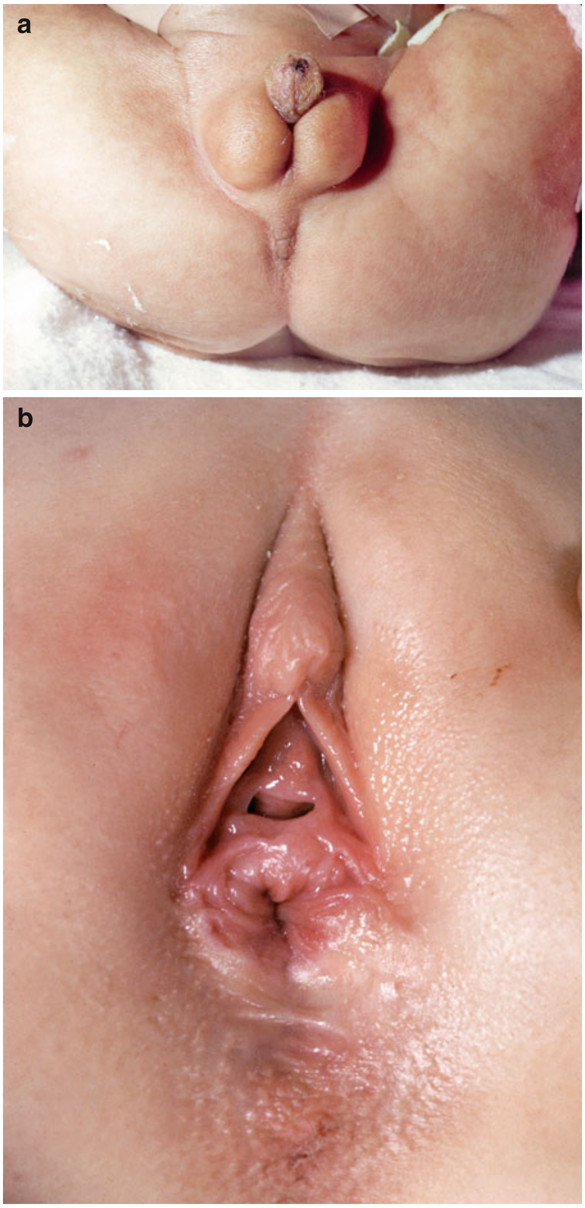

Fig. 9.5 (**a**) Anorectal malformation in boy with a rectobulbar fistula. The bifid scrotum is quite characteristic of this anomaly. (**b**) Anorectal malformation in a girl with a vestibular fistula distorting the genital anatomy

even at 6 years of age! (Fig. 9.6). Extrinsic compression of the embryo or foetus is well-described by Stephens, and is discussed in detail in Stephens et al. (2002).

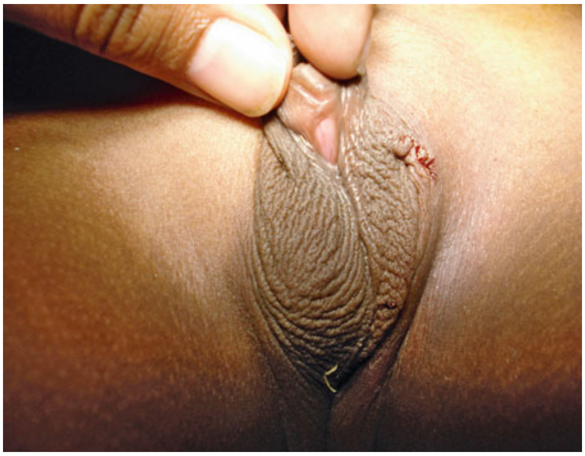

Fig. 9.6 Pressure sore over the urethra in a boy causing an abnormal urethral opening initially thought to be a urogenital sinus. The boy had secondary chordee caused by scarring from the ischaemic necrosis of the urethra, as well as atrophy of the left testis. The right heel could be folded to fit perfectly into the perineum over the abnormal urethral opening

9.6 Cloacal Maldevelopment

The cloaca is the endodermally derived common cavity for the anorectum and urogenital tracts. Failure of development of the posterior portion of the cloaca, along with incomplete separation of the urogenital tracts may lead to persistence of the primitive cloacal cavity at birth. In female infants this means all three tracts, urinary, genital and gastrointestinal, exit through a common opening. This malformation may distort the external genital development and lead to ambiguity in appearance. This is particularly the case if the external opening is very small so that the genital folds appear fused, secondary to aberrant early development, rather than androgen-induced fusion. The cloacal opening may be so small it causes urinary obstruction, with enlargement of the clitoral hood in a manner similar to distal urinary obstruction in a boy with phimosis. On physical examination, however, the erectile tissue is not enlarged, only the skin is stretched by the urinary blockage to create a phallus-like structure.

The key to recognition of this non-hormonal malformation is the very short introitus or pin-hole opening in the genital folds in a baby with an absent anus (McMullin and Hutson 1991) (Fig. 9.7a).

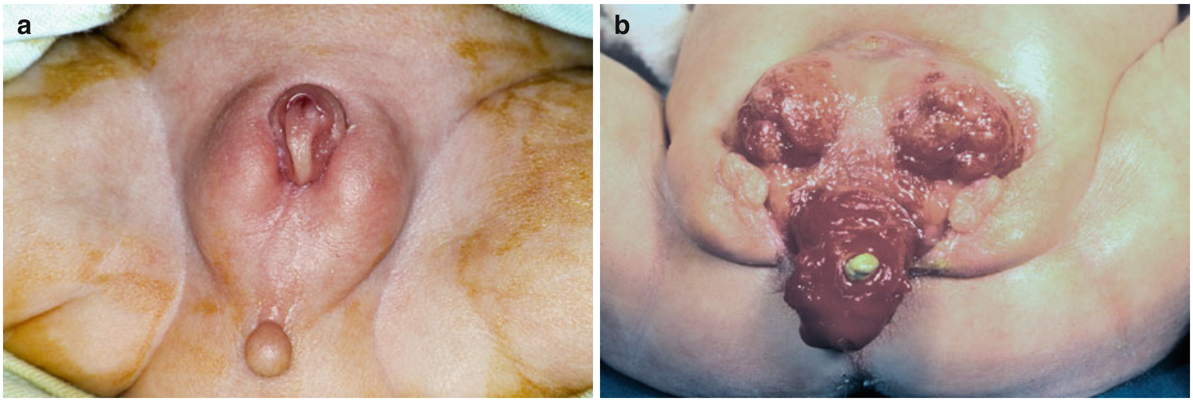

Fig. 9.7 (**a**) Cloacal anomaly with a skin tag and a tiny opening in the genital folds associated with overgrowth and stretching of the clitoral foreskin secondary to urinary obstruction. This has led to significant distortion of the external genitalia. (**b**) Cloacal exstrophy in a baby showing the exposed bowel and bladder mucosa. The partially concealed external genitalia are widely separated

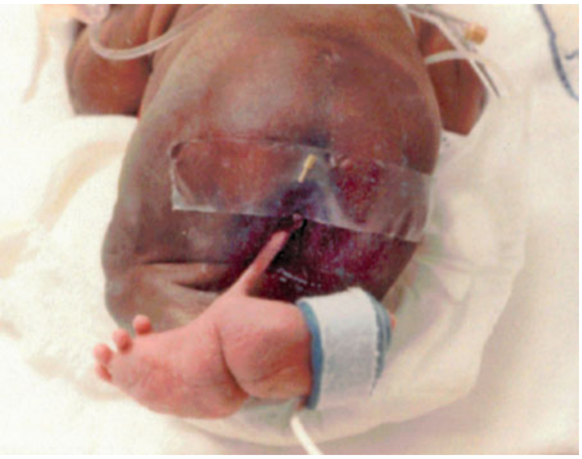

Fig. 9.8 Severe caudal regression in the rare anomaly of sirenomelia, leading to abnormal external genital development (Reproduced with permission from Stanton et al. 2003)

Arrested development at the cloacal stage, in association with abnormal mesodermal development in the lower abdominal wall causes the rare anomaly of cloacal exstrophy.

This severe malformation is associated with an unfused pelvic ring and exposure of the dysplastic midgut or hindgut on the surface between the bladder mucosal plate on each side. The genitalia are grossly distorted and widely separated into two halves (Fig. 9.7b). Not unexpectedly, there are frequently multiple other anomalies in the baby, which may impact on the plan of management. The obvious anomalies in all the pelvic organs and abdominal wall mean that these infants are easily distinguished from DSD caused by hormonal imbalance.

There are two other rare malformations of the pelvis and perineum that lead to abnormal external genitalia. The first of these is so-called caudal regression, where regulatory signals controlling growth of the lower half of the embryo are deranged. The most severe variant of this is sirenomelia, where the legs are fused like a mermaid. In this well-described but extremely rare anomaly the umbilical artery is a single vessel given off by the mid-abdominal aorta, which inhibits all distal growth by “vascular steal.” In one such case that we have seen the pelvic organs were absent, apart from the gonads, which were supported by ovarian arteries arising from the upper aorta above the abnormal umbilical artery. The anus was absent and the genital folds rudimentary and the urinary tract drained via a single dysplastic ureter directly onto the perineum (Fig. 9.8) (Stanton et al. 2003).

The final, rare anomaly of the external genitalia is caused by partial duplication of the caudal embryo, which is a form of partial conjoined twinning. There is little confusion with more common DSD, and management involves either removal of one half of the organs, or joining the duplicated structures together, depending on the precise anatomy.

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Multiple Malformation Syndromes in DSD

10

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10.1 Smith-Lemli-Opitz Syndrome (OMIM NO. 602858)

This syndrome was first described in 1964, and its main features are a variable level of developmental delay associated with microcephaly, generalised hypotonia and growth failure, dysmorphic facies, genital anomaly and syndactyly of the second and third toes (Jones 1997) (Fig. 10.1a). It is now recognised to be caused by an autosomal recessive defect in cholesterol metabolism in the DHCR7 gene.

The baby presents with microcephaly, coarse facial features and hypotonia. There is a variable degree of undervirilisation in the boys producing hypospadias and cryptorchidism (70%) (Fig. 10.1b). Fusion of the second and third toes is frequently present. There may be cardiac and visceral anomalies, and upper urinary tract abnormalities occur in 50–60% (Joseph et al. 1987). Because of the impaired steroid metabolism, the SLO syndrome presents as a DSD in males with inadequate androgens.

10.2 Denys-Drash Syndrome (OMIM NO. 607102)

Denys-Drash Syndrome results from an autosomal dominant mutation in the WT1 gene on chromosome 11 (11p13). It comprises widespread abnormalities in the structures derived from the urogenital ridge: the kidneys and the gonads. In 46,XY babies with this mutation the testes have variable dysgenesis, leading to ambiguous external genitalia or even a female phenotype (Fig. 10.2a). The dysgenetic testes are at risk of developing tumours in about 5% of

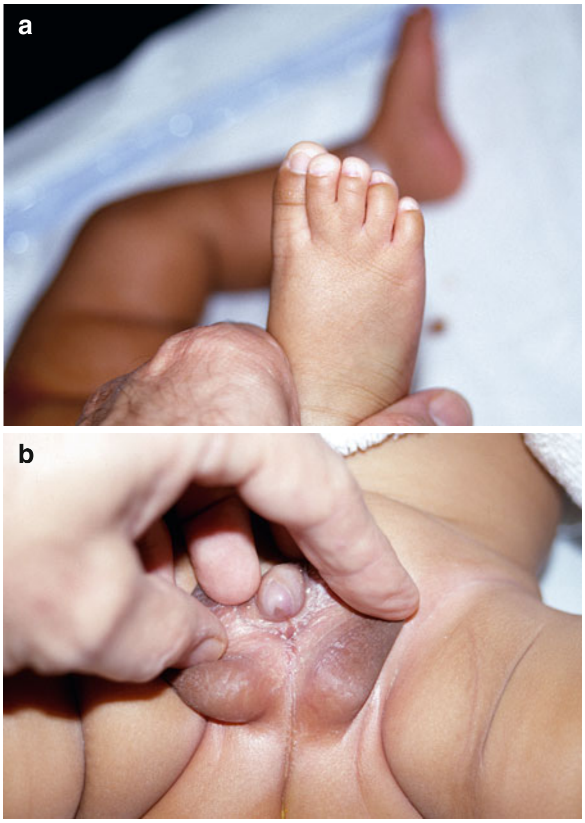

Fig. 10.1 (**a**) Syndactyly of second and third toes, which is seen in Smith-Lemli-Opitz syndrome. (**b**) Ambiguous genitalia of same patient

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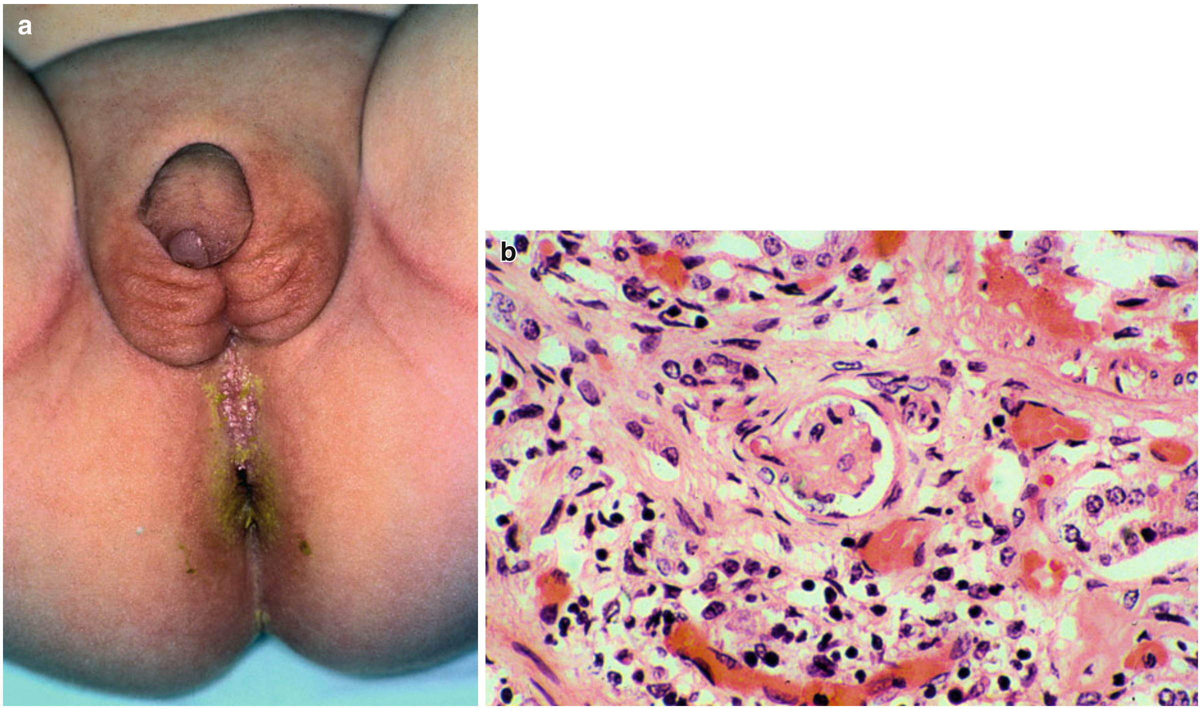

Fig. 10.2 (**a**) Ambiguous genitalia in a baby with 46, XY DSD and Denys-Drash syndrome (Reproduced with permission from Hutson and Werther 1990). (**b**) Progressive glomerulosclerosis, which is a specific feature of Denys-Drash syndrome, which led to terminal renal failure in this infant (Reproduced with permission from Hutson and Werther 1990)

patients. Renal development is also deranged, with progressive glomerulosclerosis, which causes renal failure often in the first year of life (Fig. 10.2a). There is also a high risk (about 75%) of developing Wilms' tumour (Hutson and Werther 1990).

10.3 Frasier Syndrome (OMIM NO. 60712)

Frasier syndrome is also caused by an autosomal dominant mutation in the WT1 gene, and in this case the testicular dysgenesis is more severe, leading to almost complete XY sex reversal. Such children have a female phenotype with or without minor virilisation. They carry a high risk of gonadal tumours (gonadoblastoma) and also develop focal or segmental glomerulosclerosis, which is less severe than that seen in Denys-Drash syndrome.

10.4 Opitz Syndrome

This syndrome has several other names, including hypertelorism-hypospadias syndrome, Opitz-Frias syndrome, or Opitz oculo-genito-laryngeal syndrome. The key features are hypospadias with cryptorchidism and bifid scrotum, associated with hypertelorism and a cleft between the larynx and oesophagus, secondary to abnormal separation of the respiratory bud from the front of the foregut. These babies present with 46, XY DSD associated with hypertelorism and recurrent aspiration and pulmonary difficulties if the airway anomaly is unrecognised. This can vary from tracheo-oesophageal fistula to complete laryngo-tracheo-oesophageal cleft. Affected females have no obvious DSD.

10.5 WAGR Syndrome (OMIM NO. 194072)

This is a rare syndrome characterised by a deletion of 11p13, including the WT1 gene. The key features are **W**ilms' tumour, **a**niridia, **g**enitourinary anomalies and developmental **r**etardation (W-A-G-R). The cluster of anomalies is related to the close relationship on chromosome 11 of the WT1 gene and the PAX6 ocular development gene. Genetic males with WAGR syndrome will present with dysgenetic testes with ambiguous external genitalia or occasionally female phenotype if the dysgenesis is profound. The genetic females will usually have no obvious DSD, but will present with aniridia and developmental delay, ± development of Wilms' tumour. Investigation in these girls may reveal streak ovaries and a bicornuate uterus. These patients have a high frequency of cataracts and glaucoma (>50%), as well as a high risk of recurrent tonsillitis and glue ears (Fischbach et al. 2005).

10.6 ATRX Syndrome (OMIM NO. 300032)

The defect in this disorder is a mutated helicase enzyme involved in chromatin remodelling on the X chromosome (Xq 13.3). The affected XY infant has dysgenetic testes leading to a DSD with ambiguous or female external genitalia. There is associated developmental delay and mental retardation and thalassaemia, along with other congenital anomalies.

10.7 Frequency of Multiple Malformation Syndromes

The risk of a complex multiple malformation syndrome is quite high in babies with XY DSD, and there is a serious risk of death from non-genital abnormalities (Table 10.1). We were alerted to this when we conducted a long-term follow-up of all our patients with DSD, leading to a formal study (Low et al. 2006).

We analysed all patients with ambiguous or dysmorphic genitalia over a 31-year period, and found 270 patients. Seventy of these had exstrophy/epispadias complex and were excluded, as they were easily recognisable as a subgroup and their prognosis is well known.

Of the 200 remaining patients, 26 had died (13%). We examined the medical records and post-mortem reports (20/26) of these patients to find out the cause of death. The 200 patients could be divided into those with an endocrine DSD and those with a morphological disorder of the perineum including the genitalia. There were 50 patients in the latter group, and 8 of these had died (5 with cloacal anomalies and 3 with anorectal malformations and chromosomal defects).

The 150 patients with endocrine DSD included 18 deaths (12%). There were 2 deaths out of 68 (3%) children with CAH, from hypertrophic cardiomyopathy in one baby and encephalitis with raised intracranial pressure in the other. In the 68 patients without CAH there were 16 deaths (~20%), which were evenly distributed between patients with XY DSD caused by gonadal dysgenesis (6/32, 19%), 2/14 with ovo-testicular DSD, and 8/36 (22%) with other diagnoses. The latter included Denys-Drash syndrome (2), Smith-Lemli-Opitz syndrome (2), campomelic dysplasia (1).

The babies who died with DSD had a range of severe and multiple other anomalies (Table 10.2). Most of the deaths occurred in the first year of life (23/26). The causes of death were most commonly attributed to cardiovascular anomalies (10/24), and three were secondary to renal failure (2 Denys-Drash syndrome). Four babies died from multiple life-threatening cardiac anomalies after active treatment was withheld (Table 10.3).

This review highlights the significant risk of multiple anomalies in babies presenting with 46,XY DSD, where there was a 20% mortality in a previous era before recent advances in cardiac surgery. Systematic screening should be undertaken in all babies with XY DSD where gonadal dysgenesis is

Table 10.1 Multiple malformation syndromes with genital anomaly

Syndrome	Genetics	Clinical features
Deletion 4pS	Deletion 4p	Hypertelorism, microcephaly hypospadias, cryptorchidism sacral sinus
Deletion 11qS	Deletion 11q	Trigonocephaly, cardiac defects hypospadias, cryptorchidism (50%)
Deletion 13qs	Deletion 13q	Microcephaly, high nasal bridge, eye defect, thumb hypoplasia, hypospadias, cryptorchidism
Bladder exstrophy		Exposed bladder mucosa incomplete fusion of genital tubercles
Cloacal exstrophy		Exposed colonic and bladder mucosa Imperforate anus Bifid genitalia
Cloacal anomaly (urorectal septum malformation sequence)		Cloacal anomaly with phimosis and ballooning of clitoral hood
Sirenomelia		Caudal regression with fused legs absent genitalia
Penile agenesis		Absent penis, renal anomalies
Fraser S		Cryptorchidism, auricular defect Hypospadias, cryptorchidism (♂) Bicornuate uterus, vaginal atresia, Clitoromegaly (♀)
Fryns S		Diaphragmatic hernia, coarse facies, Distal digital hypoplasia Genital duplication/atresia (♀) Hypospadias, cryptorchidism (♂)
Rapp-Hodgkin ectodermal dysplasia S		Hypohidrotic ectodermal dysplasia Hypospadias
Rieger S		Iris dysplasia, hypodontia, Hypospadias
Robinow S		Flat face, short forearms Hypoplastic genitalia
Schinzel-Giedion S		Coarse face, short forearms and legs Hypertrichosis Genital hypoplasia
Short rib-polydactyly (type II, Majewski)		Dwarfism, short ribs, polydactyly, Ambiguous genitalia
Triploidy S	Extra set of chromosomes	Growth deficiency, syndactyly 3rd–4th fingers, hypospadias, micropenis, cryptorchidism
Aarskog S		Hypertelorism, brachydactyly, Shawl scrotum
Chondroectodermal dysplasia		Short extremities, polydactyly, Nail hypoplasia, epispadias
Craniofrontal dysplasia		Craniosynostosis, shawl scrotum Hypospadias
De Lange S		Synophrys (eyebrows joined), thin upper lip, Micromelia, hypoplastic male genitalia

Table 10.2 Associated anomalies in genital anomaly

System	*n*
1. Cardiovascular Ventricular septal defect, atrial septal defect, hypoplastic left heart syndrome, transposition of great vessels, hypertrophic cardiomyopathy, anomalous pulmonary venous drainage	15
2. Respiratory Alveolar dysplasia, tracheobronchomalacia, pulmonary hypoplasia	3
3. Cranial Hydrocephalus, microcephaly	2
4. Renal Denys-Drash syndrome, hydronephrosis, Potter syndrome, renal agenesis, renal dysplasia	8
5. Vater Association	2
6. Cleft lip/palate	2
7. Musculoskeletal Femoral pseudoarthrosis, congenital dislocation of hip, talipes equinovarus, brittle bone disease, rhizomelic shortening, polydactyly	9
8. Facial dysmorphism	10

Table 10.3 Cause of mortality in the non-CAH group of GA

Probable cause of death	*n*
Cardiac failure	11
Respiratory failure	4
Renal failure	3
Decision to withhold treatment	4
Others	4

present, especially if there are other perineal anomalies such as anorectal malformation. Such screening may identify multiple anomalies, particularly of the cardiovascular system, as well as particular syndromes (Lee et al. 2006; Hughes and Malone 2005; Clericuzio 1999; Levin 2000).

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The Neonate with Ambiguous Genitalia

11

John M. Hutson

11.1 Introduction

Genital ambiguity in a baby is almost as devastating in the delivery room as a perinatal death. Now, in the context of antenatal testing, a baby born with a phenotype that does not match the gender of the antenatal testing also provokes the same confusion and concerns. Clinicians are challenged with coming to an accurate and speedy diagnosis, so that rational medical and surgical treatment can be instituted. The difficulty for clinicians is that DSDs are rare and often very complicated, which may make the clinical diagnosis difficult. To be able to diagnose these conditions it is important to understand the basic developmental steps in sexual differentiation, which have been described in the Embryology chapter (see Chap. 2). Here, we briefly re-capitulate the essential features of the development upon which the rules for clinical diagnosis are based.

Male and female embryos have similar internal genitalia until about 7–8 weeks of development. The key structure in the urogenital ridge is the regressing mesonephros, with its associated duct structures in the lateral edge of the ridge and the developing gonad on its antero-medial surface. The mesonephric or Wolffian duct develops first as the excretory duct of the primitive renal tract. The paramesonephric duct or Müllerian duct develops as an invagination of the peritoneum in the lateral edge of the urogenital ridge cranially and migrates to the cloaca, crossing the Wolffian duct to become fused with the contra-lateral Müllerian duct (see below).

Testis development begins at about 8 weeks, with the production of MIS/AMH and androgen. Under the exocrine action of androgens secreted down the Wolffian duct, it differentiates into epididymis cranially vas deferens in the middle section, and gives a bud which forms the seminal vesicle caudally. The high concentration of testosterone within the duct obviates the need for conversion to dihydrotestosterone (DHT).

Secretion of MIS/AMH down the ducts causes regression of the adjacent Müllerian duct, which would, in the absence of the hormone, form the Fallopian tube, uterus and the upper vagina (Fig. 11.1). The vagina itself is derived from endoderm of the urogenital sinus that is stimulated to grow into the vaginal plate by the arrival of the Müllerian ducts to produce the sino-vaginal bulb. Development of the vaginal plate is inhibited by circulating androgens (after conversion to DHT), and therefore the degree of lower vaginal development is inversely related to the amount of androgens (i.e. DHT) to which the foetus is exposed (Fig. 11.2).

With differentiation of the testis at approximately 8 weeks of development, the amount of testosterone circulating in the bloodstream in an endocrine manner is relatively small, because the total number of Leydig cells is still small. This has led to some special adaptations to increase the relative concentration of hormones into the active endocrine range. To masculinise the internal genitalia the hormones are secreted in an exocrine manner down the Wolffian duct, thereby exposing the ducts to very high local concentrations, but only on the side of the testis in the rare anomalies where there is only one testis. To virilise

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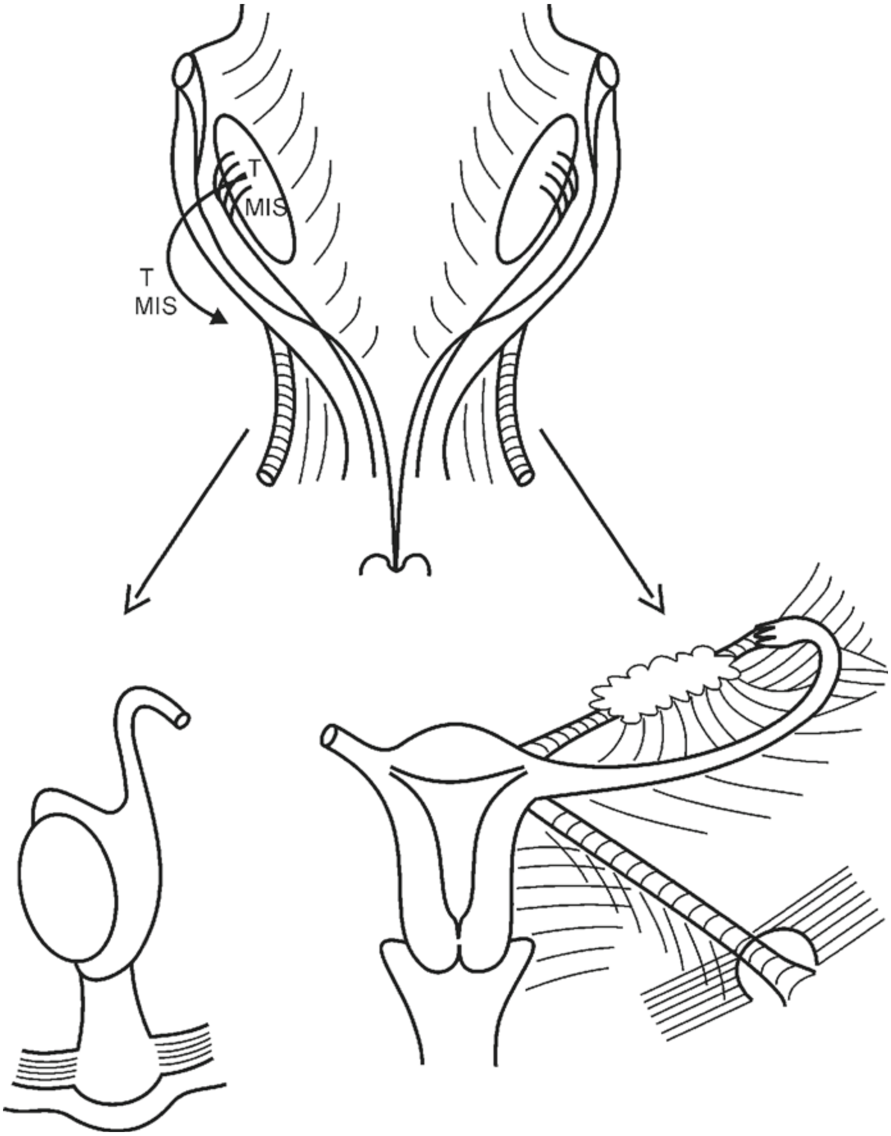


Fig. 11.1 Ambisexual urogenital tracts at 7 weeks of gestation, showing gonad with adjacent Wolffian and Müllerian ducts. Caudally there is an extra fold extending from the urogenital ridge to the anterior abdominal wall: the genito-inguinal ligament or gubernaculum. Male development is shown on the right side of the embryo, where testosterone and MIS/AMH are secreted by the developing testis and pass in an exocrine manner down the Wolffian duct to masculinise the Wolffian duct itself and cause regression of the adjacent Müllerian duct. By 12–15 weeks of gestation the epididymis has formed from the proximal Wolffian duct and the gubernaculum has undergone the 'swelling reaction', which enables the enlarged gubernaculum to hold the testis near the inguinal region as the abdomen enlarges. The cranial suspensory ligament has regressed. On the left side, absence of male hormones triggers Wolffian duct regression, while the Müllerian duct develops into Fallopian tube, uterus and upper vagina. The regressing mesonephros leaves the ovary on a mesentery which persists cranially as the suspensory ligament and laterally as the broad ligament. The gubernaculum elongates in proportion to growth to become the ligament of the ovary and the round ligament, which ends just outside the external inguinal ring

the external genitalia a different strategy is used, with conversion of testosterone into DHT (Fig. 11.3). The external genitalia require DHT because the concentration of testosterone itself is too low. Some actions of testosterone on sexual dimorphism of the brain, for example, are thought to be mediated by conversion of testosterone to oestrogen. The net effect of conversion of testosterone to another steroid metabolite is to

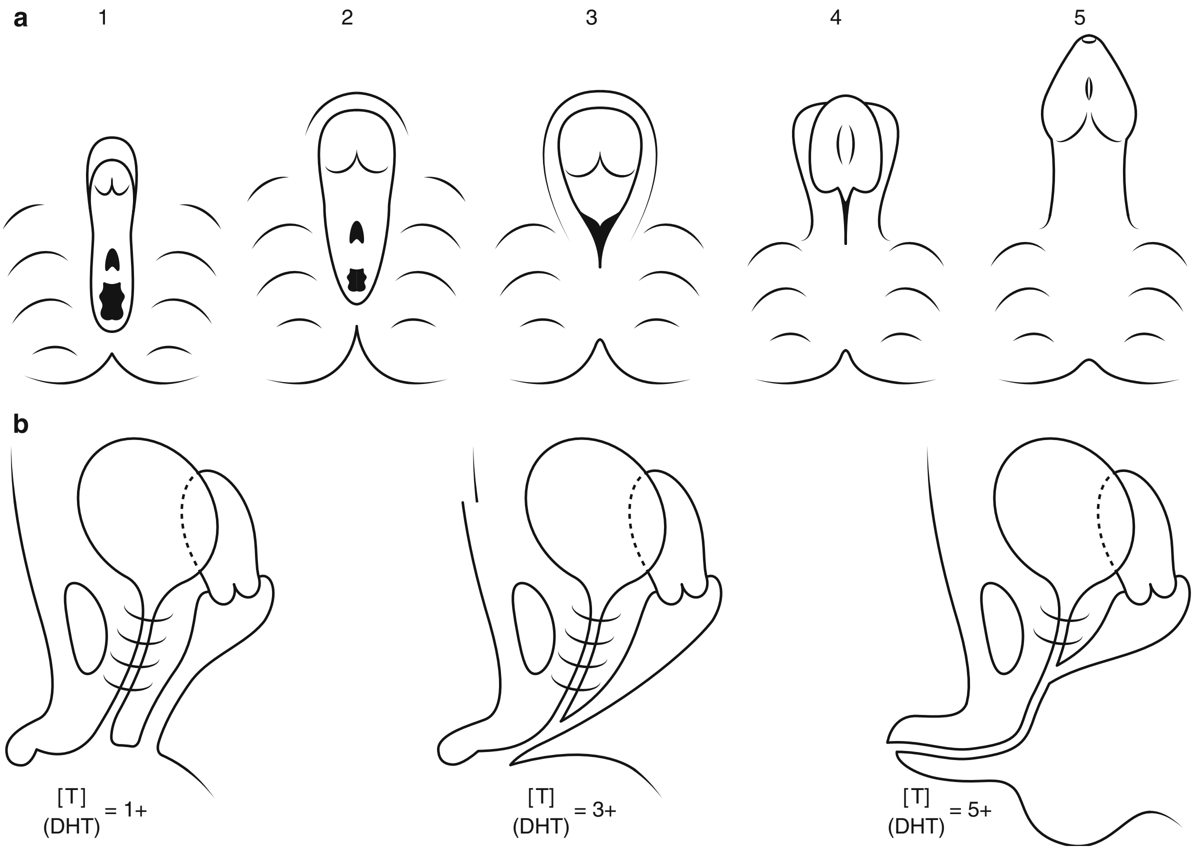


Fig. 11.2 (**a**) The Prader classification of the degree of virilisation of the external genitalia is from 0 (normal female) to 5 (normal male appearance). Prader 1 is clitoromegaly alone. Prader 2 is clitoromegaly and a funnel-shaped urogenital opening showing two orifices (urethra and vagina). Prader 3 is more virilised where only one opening is visible inside the urogenital opening. Prader 4 is more masculinised still, where the opening is on the proximal shaft of the enlarged phallus. The increasing virilisation from 1 to 5 is directly related to levels of androgens the foetus is exposed to, and also inversely related to the degree of regression of the developing lower vagina. (**b**) The regression of the lower part of the vagina is directly related to the amount of androgens present and the degree of external genital virilisation

increase the effective endocrine concentration so that it can act on the receptors in the remote target organs significantly.

The testicular Leydig cells also produce insulin-like hormone3 (INSL3), which stimulates development of the genito-inguinal ligament, or gubernaculum. Growth of the gubernaculum in the trans-abdominal phase of descent is augmented by the action of MIS/AMH. This leads to a very tight relationship between production of MIS/AMH and the first phase of testicular descent (Fig. 11.1). The second phase of testicular descent, from the inguinal region to the scrotum, is regulated by androgens, which act to some extent locally, but also indirectly via the genito-femoral nerve. The nerve releases calcitonin gene-related peptide (CGRP) from its sensory nerve endings to provide a concentration gradient for migration of the gubernaculum to the scrotum (Fig. 11.4).

Production of the enzyme 5-α reductase-2 enables conversion of testosterone to DHT in the external genitalia. DHT binds approximately ten times more avidly to the androgen receptor than testosterone itself. This stimulates development of the external genitalia with growth of the genital tubercle and development of the male anterior urethra until it opens on the tip of the glans penis. It also stimulates fusion of both the inner and outer genital folds, the latter forming the scrotum. Finally, circulating androgens stimulate the development of the posterior urethra to form the prostate, and at the same time prevent development of the vaginal plate into the lower vagina.

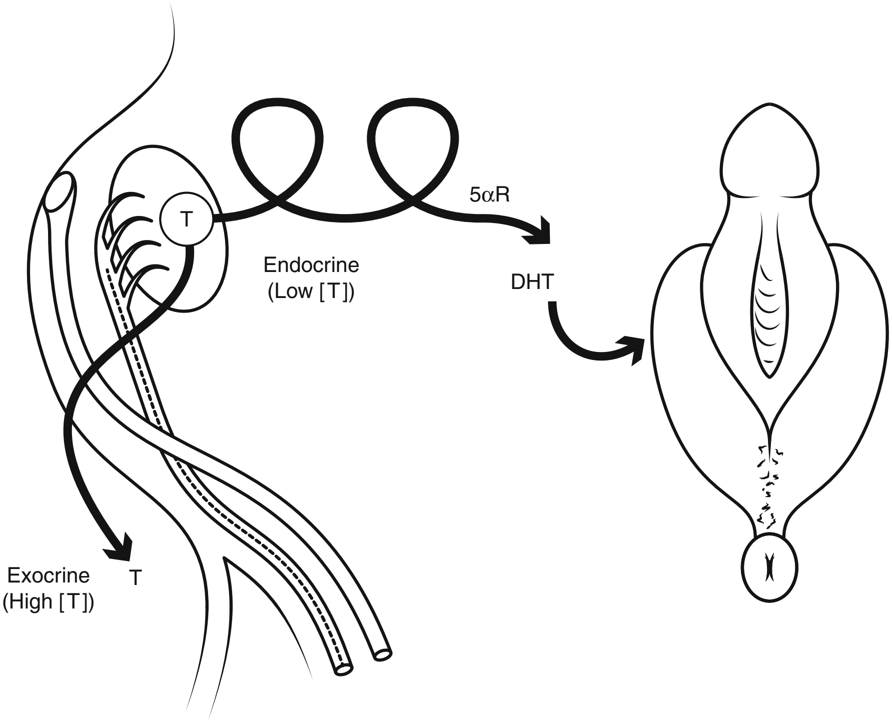


Fig. 11.3 The internal ducts respond to exocrine secretion of testosterone and MIS/AMH down the mesonephric (Wolffian) duct at high concentrations of both hormones. By contrast, the external genitalia are exposed to testosterone levels that are too low for normal function, probably related to the minute size of the developing testis. Conversion of testosterone to dihydrotestosterone (*DHT*) by the enzyme 5-alpha reductase overcomes the low levels, as DHT binds ten times more tightly to the androgen receptor. This increases the effective androgen concentration ten-fold at this crucial time for external genital development

Sexual dimorphism of the external genitalia is effectively completed by 12–15 weeks of gestation; however the phallus continues to grow in response to androgens throughout pregnancy. The initial production of testosterone between 8 and 12 weeks is probably controlled by chorionic gonadotrophin, but after this time the foetal hypothalamus and pituitary takeover the regulation of androgen production (Fig. 11.5). Later, in foetal development, the role of DHT becomes less important as the testes enlarge and the amount of testosterone produced increases. During this time, descent of the testis in response to testosterone and closure of the processus vaginalis occur, both under the combined action of testosterone and CGRP released by the genito-femoral nerve.

With a full understanding of normal and abnormal development, the diagnosis in babies with a genital anomaly can be predicted using a set of rules (Low and Hutson 2003).

11.2 Diagnostic Rules and Clinical Significance (Table 11.1)

1. Testes descend (through the abdominal wall and down to the scrotum), but ovaries do not. The presence of a palpable gonad, therefore, indicates the presence of testicular tissue on that side, and also implies the presence of the SRY gene somewhere in the genome (Fig. 11.6). Prolapse of an ovary into an inguinal hernia can occur, but this is extremely rare in the first week of life.
2. Testicular descent is tightly linked to Müllerian duct regression. When two palpable testes are present this means that there will be no uterus. When a single testis is palpable it indicates that there should be a Wolffian duct on the ipsilateral side, but there should be no Müllerian duct on that side. In the absence of either palpable gonad, the gonadal and ductal status remains unknown.
3. The presence of the uterus (on digital examination or ultrasonography) indicates the absence of MIS/AMH between 8 and 12 weeks of development (Fig. 11.7). This means that the testes are either missing or very dysgenetic. In the presence of normal male sexual development it indicates the absence of MIS/AMH or its receptor in the rare syndrome of persistent Müllerian duct syndrome.
4. Regulation by male hormones of the internal genitalia is exocrine, and hence is confined to the side that contains a testis (Fig. 11.8) (Tong et al. 1996; Ben-Meir and Hutson 2005). This can be seen in

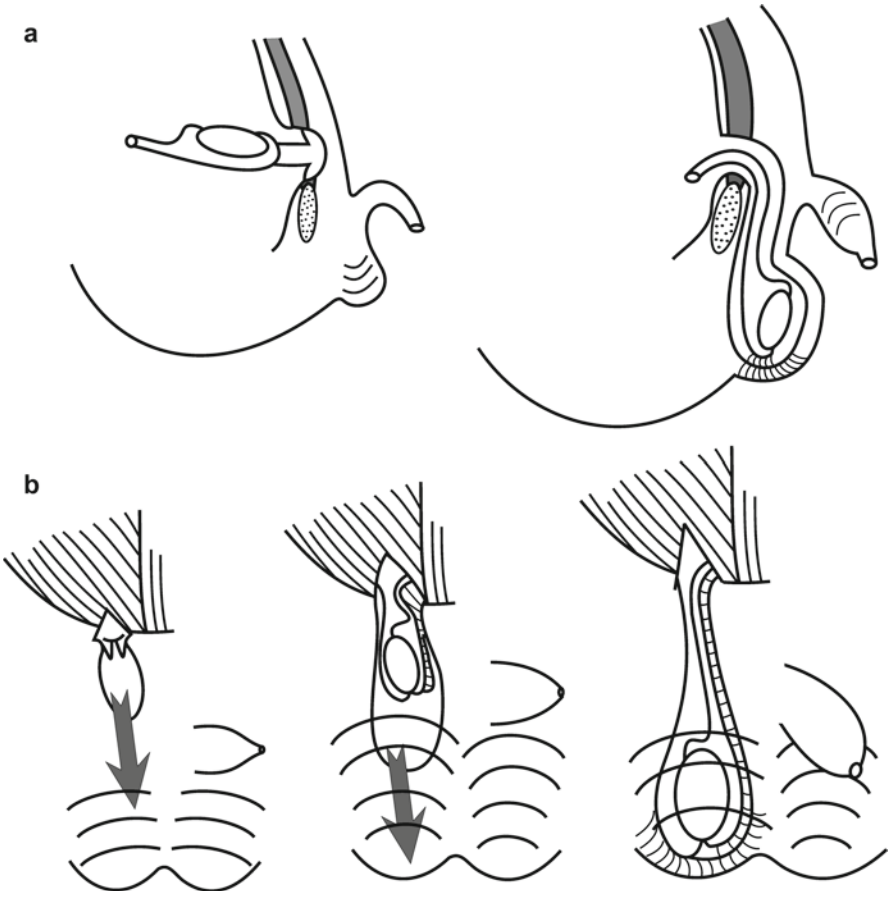


Fig. 11.4 The last morphological phase of sexual differentiation is descent of the testis. The first phase of so-called transabdominal descent occurs between 8 and 12–15 weeks of development, with enlargement of the gubernaculum ('swelling reaction'), which holds the testis nearer to the groin than the ovary (see Fig. 11.1) in response to INSL3. (**a**) At the end of the first phase the testis is anchored to the future inguinal canal as the processus vaginalis develops inside the gubernaculum. During the inguino-scrotal phase (25–35 weeks) the gubernaculum migrates to the scrotum, by mechanisms not yet fully understood, allowing the processus to elongate inside it so the testis can reach the scrotum within an extension of the peritoneal cavity. This is shown in sagittal section. (**b**) Viewed from the front, the gubernaculum, the end of which is gelatinous mesenchyme, migrates across the pubis and into the scrotum, within which it then becomes secondarily attached. The proximal processus vaginalis obliterates, leaving the testis inside a satellite peritoneal cavity within the hemiscrotum

the gonadal asymmetry that occurs in ovo-testicular DSD and in 45,X/46,XY mixed gonadal dysgenesis, where the Wolffian duct is only present on the side of the testis and the ipsilateral Müllerian duct is absent, due to the local exocrine action of MIS/AMH (Fig. 11.8).

5. Circulating androgens from an abnormal adrenal gland or other sources are insufficient to allow development of the male internal genitalia. This means that even in babies with very severe masculinisation in CAH, there is no preservation of the Wolffian duct (Fig. 11.3).
6. External virilisation is directly proportional to the amount of androgens (Fig. 11.2a). Any enlargement of the clitoris, even in an otherwise phenotypically normal female, indicates abnormal foetal exposure to androgens. Genotype, in this case, may be either 46,XX with virilisation or 46,XY with under-virilisation.
7. The degree of external masculine development is inversely proportional to the degree of lower vaginal development (Fig. 11.2b). In a baby with ambiguous genitalia, the greater the degree of external virilisation the shorter will be the vaginal length.

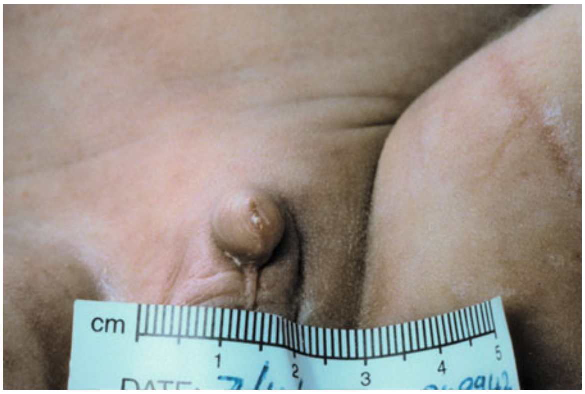


Fig. 11.5 The external genitalia respond to androgens between 8 and 12–15 weeks of development for normal masculinisation, and beyond that no further masculinisation of the urethra and labio-scrotal folds occurs. The phallus, by contrast, can grow in response to androgens right up to delivery. Early androgen production is autonomous and/or stimulated by placental hCG, until about 15 weeks, when the foetal hypothalamic-pituitary axis takes over regulation of testicular function. Baby boys with a hypothalamic or pituitary disorder, therefore, have normal male external development but a micro-penis

8. Circulating androgens only masculinise the external genitalia (except for the phallus) between 8 and 12 weeks of development (Fig. 11.5). Absence of androgens beyond this time leads to micropenis and undescended testes in a baby with otherwise normal masculine external genitalia. This is seen in abnormalities when the gonadotrophin production is abnormal, such as pituitary anomalies. Androgen deficiency between 8 and 12 weeks leads to an unfused scrotum, but androgen deficiency after this time only prevents growth of the penis. The phallus can and does respond to androgens throughout pregnancy. An enlarged phallus without fusion of the scrotum or a masculine urethra indicates exposure to androgens only in the second half of pregnancy.
9. Use of the word '*hypospadias*' assumes the affected infant is a boy, and should only be diagnosed at birth (without investigation) when both testes are fully descended into a fused scrotum (Fig. 11.9) (Tong et al. 1996). Normal sexual development of the rest of the external genitalia demonstrates that this boy has an abnormality of the penis and urethra but not a global abnormality of sexual development. Failure of urethral development or scrotal fusion in association with undescended testes is a sign of under-virilisation in early embryogenesis, and hence these babies should be investigated immediately for a DSD.
10. Genital anomalies may be caused by non-endocrine mechanisms (Fig. 11.10). These babies have physical abnormalities that lie outside the normal spectrum of development between male and female. Such examples include cloacal anomaly, cloacal exstrophy, bladder exstrophy, vaginal atresia and penile agenesis (see Chap. 9).

11.3 Clinical Approach to a New Baby with Ambiguous Genitalia

11.3.1 History

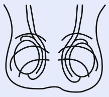
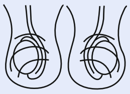
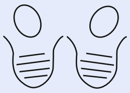
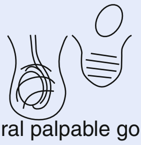
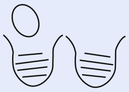
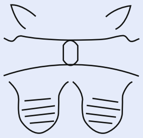
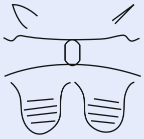
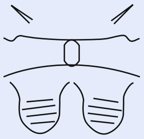
A careful history may reveal maternal steroid ingestion, an androgen-producing tumour with symptoms of maternal virilisation or a positive family history of a DSD.

11.3.2 Clinical Examination

Using the ten rules described above it is usually possible to determine the likely cause of the problem, or produce a very short differential diagnosis. Usually, the baby has a genital appearance that is in-between normal male and normal female. The phallus is larger than a normal clitoris, but smaller than a normal penis (Phillip et al. 1996; Oberfield et al. 1989). The first step is to document the degree of masculine development using the semi-quantitative Prader scale. This is a five-point scale from zero (normal female appearance) to five (normal male appearance) that gives a reasonably accurate estimation of the amount of androgen exposure between 8 and 12 weeks of development. It also indicates the likely amount of lower vaginal regression. Recently, Ahmed and Rodie (2010) have suggested a modified scale known as the external masculinisation score (EMS).

The site of the urogenital opening needs to be identified. The labio-scrotal folds on either side of the urogenital opening should be gently pulled open, as this enables the examiner to look into the urogenital sinus (Fig. 11.11). The funnel-shaped opening is characteristic of DSD, but rare in children with simple hypospadias, where the opening is usually very small. Where a

Table 11.1 The diagnostic significance of gonadal position and presence of uterus in babies with ambiguous genitalia

Gonadal position	Uterus	Predicted diagnosis	Comments
 2 testes, fused scrotum	Absent	• Normal male	Expected karyotype XY Rarely, in PMDS, uterus and tubes are present
 2 testes, bifid scrotum	Absent	• Undervirilized XY	TH with bilateral ovotestes possible but less likely; ovotestes are likely to be maldescended
 2 testes, both high, bifid maldeveloped scrotum	Likely absent	• Undervirilized XY • TH with ovotestes • XY Gonadal Dysgenesis (dysplastic testes)	
 Bilateral palpable gonads, *asymmetrical* descent	Hemiuterus likely present	• TH with 1 testis, 1 ovotestis, ovary ± hernia	MGD with 1 testis, 1 streak ovary may present with a hernia mistaken as a palpable groin gonad
 Gonadal *asymmetry,* only 1 palpable gonad	Hemiuterus likely present	• TH with 1 testis, 1 ovary/ovotestis • MGD with 1 testis, 1 streak ovary	
 No palpable gonads, external rings open	Absent Present	• Undervirilized XY • XY gonadal dysgenesis • TH with 1 testis, 1 ovotestis or 2 ovotestes	An open external ring when gonads are non-palpable will be a clue to the presence of a high testis
 No palpable gonads, *asymmetry* with 1 ring open, 1 closed	Hemiuterus likely present	• TH with ovary, ovotestis • MGD with undescended testis, streak gonad	XX karyotype with normal steroid profile likely to suggest TH
 No palpable gonads, both external rings closed	Likely present	• Virilized XX • XY gonadal dysgenesis	Predict XY karyotype and raised 17 OHP

PMDS persistent Müllerian duct syndrome, *TH* true hermaphrodite, now known as ovo-testicular DSD *MGD* mixed gonadal dysgenesis, *17 OHP* 17 hydroxyprogesterone. Reproduced with permission from (Low and Hutson 2003)

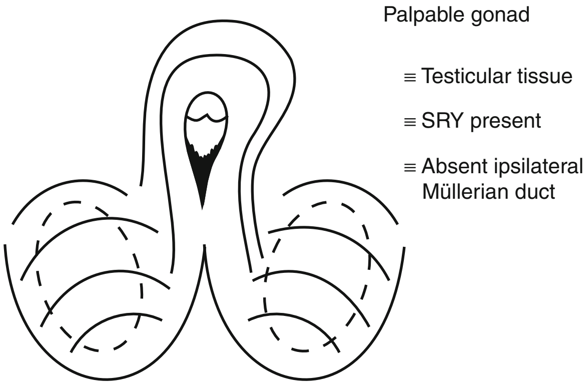


Fig. 11.6 If gonads are palpable in the labio-scrotal folds or groin it can be assumed that they are testes. Moreover it implies the presence of SRY to trigger testicular development. In addition, it can be predicted that the ipsilateral Müllerian duct will be absent, as trans-abdominal testicular descent and Müllerian duct regression are very tightly linked

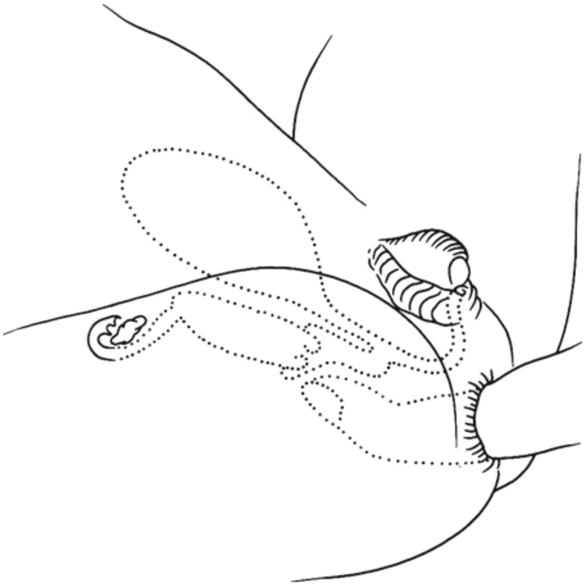


Fig. 11.7 Palpation of the uterus and cervix on rectal examination (with the little finger) is possible in term babies. (It feels like the rubber or eraser on the end of a lead pencil)

funnel-shaped opening is present it is important to search at the cranial end of the funnel for mucosal tags with a slightly bluish colour, which indicates the presence of the hymen, and confirms that a vagina is present.

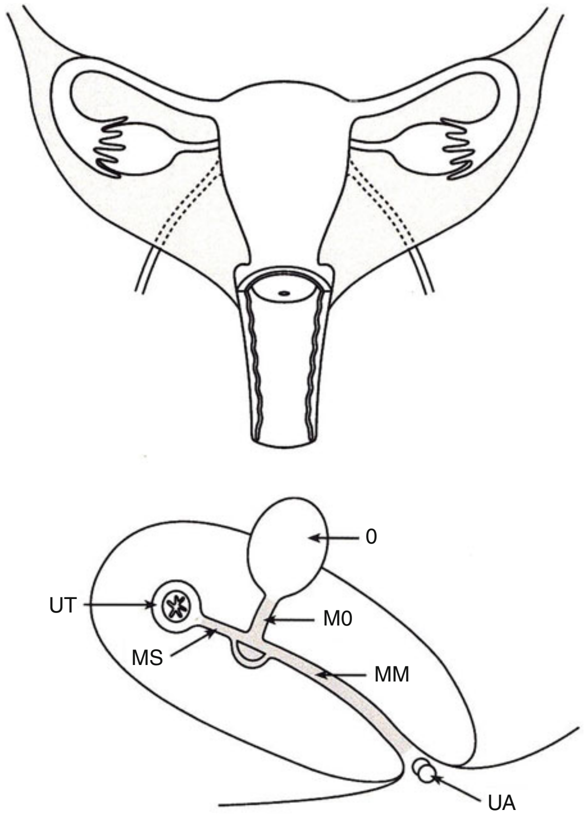
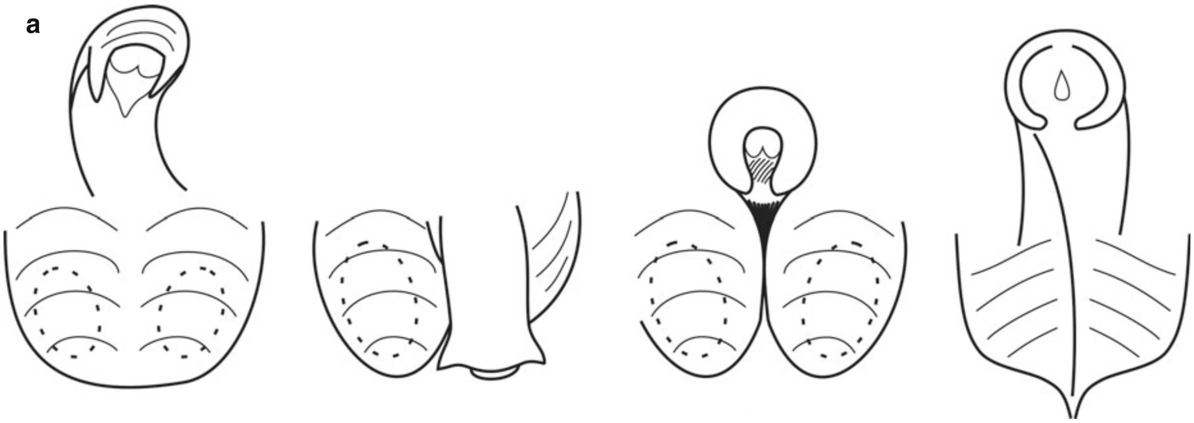


Fig. 11.8 Drawing of broad ligament (*shaded*) in adult female human shown from the back (**a**), and from the side (**b**). *Ut* uterine tube, *O* ovary, *MO* mesovarium, *MS* mesosalpinx, *MM* mesometrium, *UA* uterine artery (Redrawn from Gray's Anatomy (39th edn) and reproduced with permission from Miller et al. 2004)

The next step is to determine whether or not there are gonads present by palpation of the inguino- scrotal folds and the inguinal region. Palpable gonads are always testes except in the rare circumstances of ovo-testicular DSD, where the gonad may be an ovo-testis. It is possible for ovaries to prolapse into an inguinal hernia, but this is an extremely rare presentation in a neonatal female with normal genitalia, so this possibility can be discarded. A palpable testis also indicates absence of the uterus on that side. There are three possible scenarios. In the first instance both gonads are palpable and symmetrical. This occurs in babies that have XY chromosomes and have formed testes, but there has been inadequate testosterone production (gonadal dysgenesis) or action. In the second instance, only one gonad is palpable. This indicates that at least one testis is present, although the other gonad may be an ovary, an ovo-testis or a streak gonad. Gonadal asymmetry is very characteristic of ovo-testicular DSD and 45,X/46,XY mixed gonadal dysgenesis. In the third instance, neither gonad is palpable, and in this circumstance, the status of the gonads and the internal genital ducts is unknown. Further information on whether or not



2 testes
fused scrotum
≡ hypospadias

1 testis
bifid scrotum
≡ ? DSD
(MGD/O-T DSD)

2 testis
bifid scrotum
≡ ? DSD
(? Androgen
deficit/blockade)

No testis
fused scrotum
≡ ? DSD
(CAH)

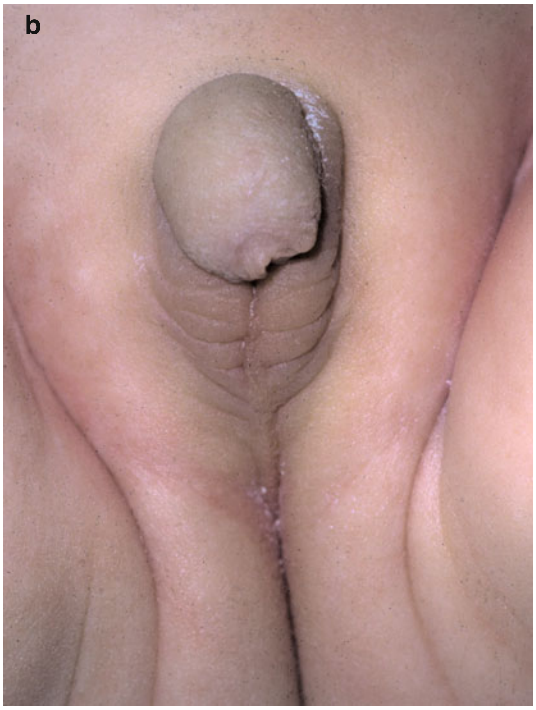


Fig. 11.9 (**a**) A diagnosis of 'hypospadias' should only be made after excluding patients with DSD. A safe rule is to assume that simple hypospadias is present *only* when there is a fused scrotum containing 2 testes. Patients with a single gonad may have MGD or ovo-testicular DSD; patients with a bifid scrotum containing gonads may have defects in androgen production or action; patients with no palpable gonads may have Prader 5 CAH (!). (**b**) A newborn genetic female with congenital adrenal hyperplasia (21-hydroxylase deficiency) with an empty 'scrotum' and trivial 'hypospadias'. The absence of gonads differentiates this clinical picture from a male with simple hypospadias without further investigations

a testis is present can be obtained by very careful palpation of the external inguinal ring. If there is a testis within the inguinal canal, the external inguinal ring is nearly always open and is palpated as an inverted V-shaped defect in the external oblique aponeurosis, adjacent to the pubic tubercle. By contrast, when the external inguinal ring is closed, it is much more likely that there is no testis on that side at all, and that the internal anatomy is

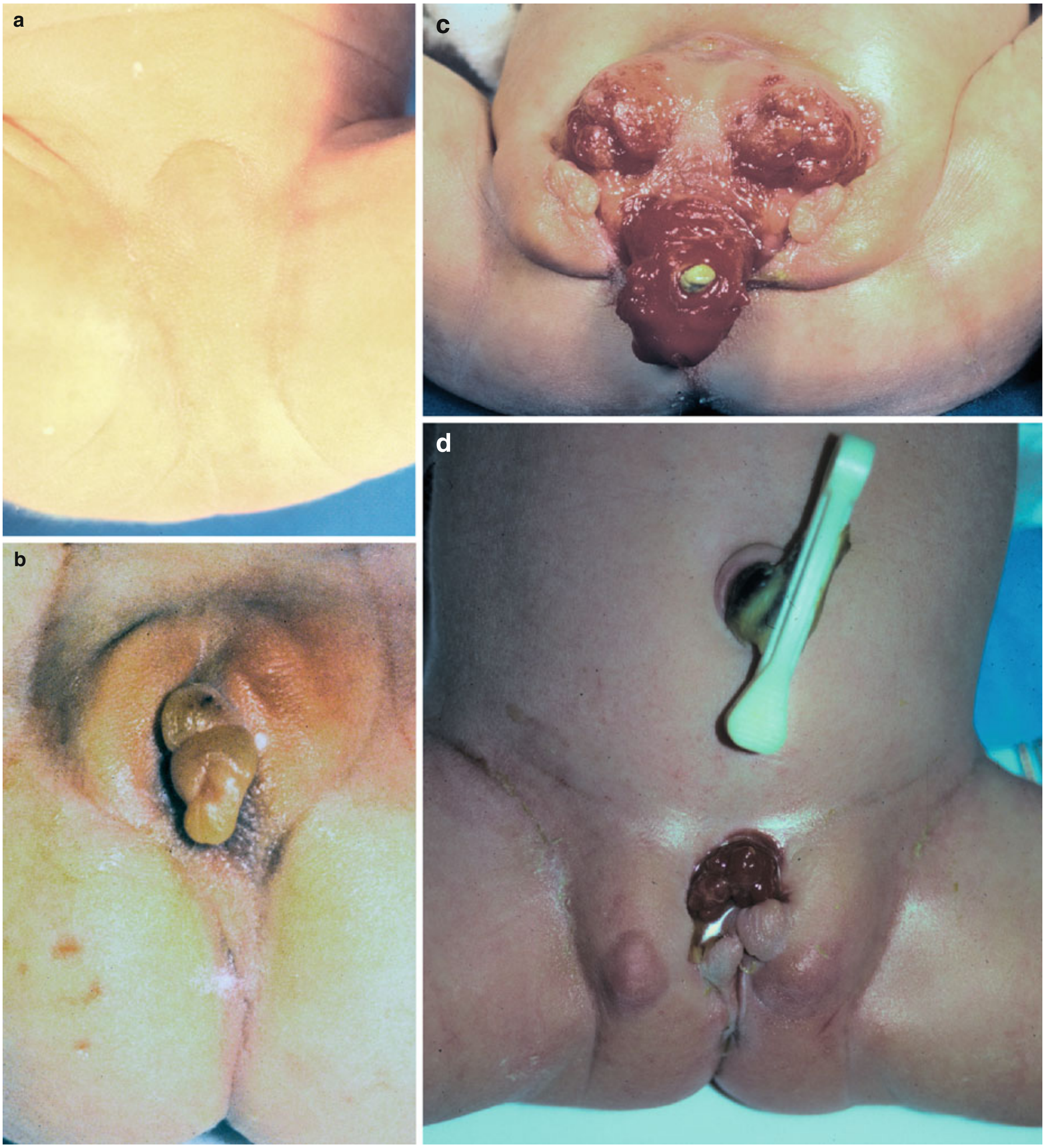


Fig. 11.10 Abnormalities of the external genitalia caused by non-endocrine mechanisms. (**a**) Penile agenesis with about external genitalia and anus; (**b**) Cloacal anomaly; (**c**) Cloacal exstrophy; (**d**) Bladder exstrophy

feminine (Fig. 11.12).There may be ovaries or extremely dysplastic testes. A rectal examination with a well-lubricated little finger can be performed as long as the baby is not premature. The uterus and cervix can be palpated as a cord-like structure behind the bladder (Fig. 11.7). (The cervix feels like the eraser on the top of a pencil).

One should now look for other clues on general physical examination. The degree of pigmentation of the genital skin should be noted, as hyper-pigmentation is seen in CAH, from the excess melanin-stimulating hormone production. The presence of dysmorphic features may indicate a multiple malformation syndrome,

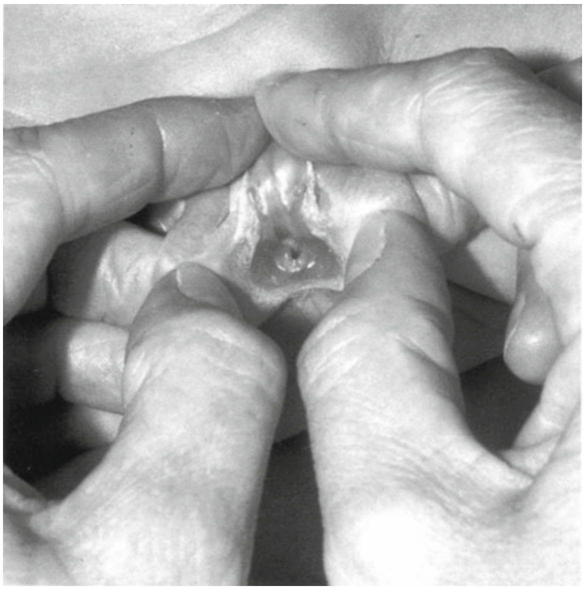


Fig. 11.11 The labio-scrotal folds need to be pulled open so that the funnel-shaped urogenital sinus can be inspected. If a hymen is present at the apex of the funnel it will appear as slightly bluish mucosal tags

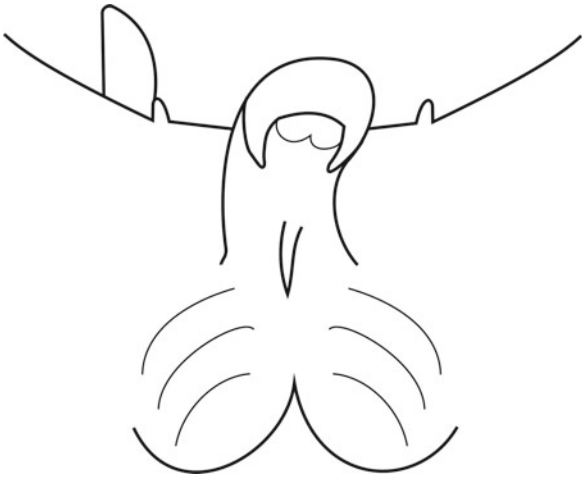


Fig. 11.12 When no gonad is palpable in the genital folds the external inguinal area needs careful examination. If the external inguinal ring, as shown on the patient's left side, is closed, then a testis in the canal is very unlikely. By contrast, if a triangular defect is palpable, indicating that the external ring is open (seen on the right), then it is very likely that the inguinal canal contains a testis

particularly in the presence of palpable gonads (see Chap. 10). Signs of a systemic illness should also be sought, as this may indicate a metabolic problem, such as adrenal insufficiency, although this does not normally present until 1–2 weeks of age. The presence of other anatomical abnormalities in the perineum, such as imperforate anus, suggests a morphological anomaly unrelated to abnormal hormones.(See Chap. 9).

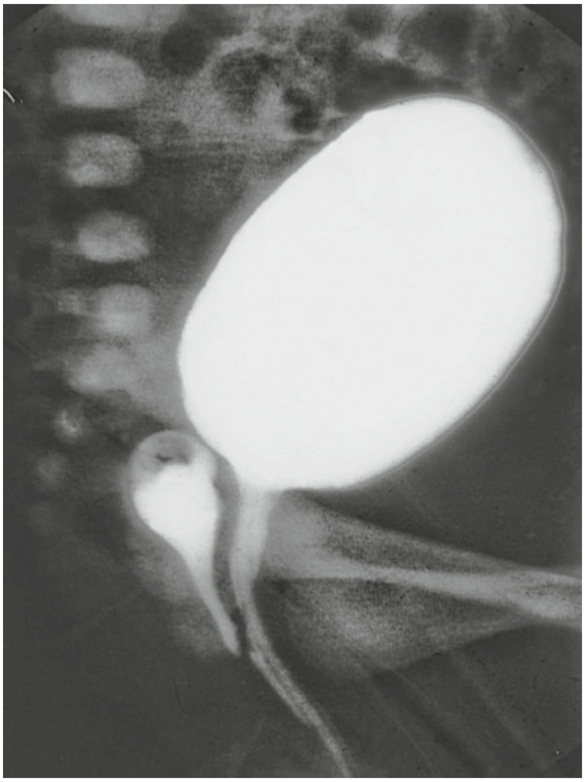


Fig. 11.13 Urogenital sinugram to show the common urogenital sinus distally bifurcating into urinary and genital tracts

11.4 Investigations

11.4.1 Medical Imaging (See Chap. 14 for Detailed Description)

Pelvic ultrasonography or a urogenital sinugram will usually confirm the predicted internal genitalia. Pelvic ultrasonography can detect the presence of the neonatal uterus, although this is not as useful after the neonatal period as the uterus shrinks in size with the fall in reproductive hormones. Ultrasonography may also demonstrate the location of intra-abdominal gonads, and is useful to check that the urinary tract is normal.

A contrast study through the urogenital sinus will confirm the presence of and delineate the anatomy of the lower vagina (Fig. 11.13). Undiluted water-soluble contrast medium should be used to prevent contamination of the peritoneal cavity with barium. It is easy to miss the vagina if a standard micturating cystourethrogram is performed, as the catheter may only outline the bladder. In those circumstances, the musculature around the urethra may compress the opening of the vagina. If a single catheter technique is used the contrast medium should be injected retrogradely. Sometimes it is necessary to insert a tiny balloon catheter to distend the distal urogenital sinus sufficiently. The second useful method is to pass a second catheter, as the second catheter nearly always will pass into the opposite structure that has been cannulated by the first catheter. The two-catheter technique will usually allow demonstration of both the urinary and the genital tracts.

11.4.2 Endoscopy

On occasions, the contrast X-ray fails to demonstrate a vaginal opening, and it is necessary to perform a cystoscopy. In children where the vagina is present, its opening into the urinary tract is heralded on endoscopy by small mucosal folds, which represent the hymen. These folds may flutter in the current of water perfusing the cystoscope, and often look like seaweed or an anemone underwater. The opening of the vagina is always in the centre of these folds, and it can be demonstrated by the insertion of a ureteric catheter. The size of the cavity can be determined by direct measurement, or by injection of contrast medium and fluoroscopy.

11.4.3 Laparoscopy (See Chap. 18 for Detailed Description)

This investigation is not required in most cases, as the external anatomy, complemented by an ultrasound of the internal genitalia and hormonal investigations, is usually diagnostic. Laparoscopy is most useful in patients with 45,X/46,XY mixed gonadal dysgenesis or ovo-testicular DSD, where it may be necessary to excise or biopsy the gonad, and to determine the precise anatomy of the internal genital ducts. This is particularly true if there is a hemi-uterus and single Fallopian tube. The details of laparoscopic management are given in Chap. 18.

11.4.4 Initial Laboratory Investigations

The serum electrolytes, glucose and 17-OH progesterone should indicate whether the baby might have CAH. Other hormone levels, including serum testosterone (Leydig cells), FSH, LH (pituitary), and MIS/AMH (Sertoli cells) will help determine gonadal function. The serum ratio of testosterone/DHT is useful to distinguish between 5-alpha reductase type-2 deficiency and androgen resistance in PAIS. Urgent fluorescent in situ hybridisation (FISH) to detect Y chromosome sequences will indicate whether a Y chromosome is present. A full karyotype will be required to distinguish chromosomal and aneuploidy DSD.

Depending on initial results, an hCG-stimulation test may be needed to determine the presence of androgen-producing testicular tissue, while the serum DHT level may help to document the uncommon case of 5-alpha reductase-type2 deficiency. An ACTH-stimulation test will document any steroid biosynthesis anomaly in the testis or adrenal gland. Twenty-four hour urine collection permits a full steroid profile for defects in steroid biosynthesis by the use of gas chromatography and mass spectrometry.

On specific indications, specific genetic screening may be required for mutations in certain genes, such as the androgen receptor gene.

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12

DSD Later in Childhood

John M. Hutson and Garry L. Warne

12.1 Introduction

When the external genitalia are ambiguous at birth a diagnosis of DSD is usually suspected immediately, particularly if the appearance is really intermediate between normal male and normal female. There are situations, however, when the presentation is much later in childhood. This occurs in two special circumstances, such as when the external genital anomaly is so subtle that it escapes immediate attention at delivery and at the new-baby examination. The second situation is where the external genitalia seem normal, and events lead to the internal genitalia being examined, and then found to be discordant with expectation. The common surgical scenarios are described in Table 12.1, and are discussed below. In a third major group of conditions, the DSD presents when the child develops precocious puberty.

Table 12.1 Surgical presentations of DSD during childhood

	Clinical scenario	Likely DSD
1	*Inguinal hernia*	
	Female with hernia containing testis	CAIS, GD
	Male with hernia containing ovo-testis	O-T DSD
	Male with hernia containing uterus	PMDS
	Male with absent vas deferens at herniotomy	Cystic fibrosis/ Rokitansky sequence
2	*Cryptorchidism*	
	Uterus found with testis	PMDS
	Ovo-testis found	O-T DSD
	Streak gonad found (± fallopian tube)	MGD, GD
3	*Laparoscopy*	
	Abnormal/absent ovaries	GD, Turner syndrome
	Absent uterus/fallopian tube	Rokitansky sequence
4	*Hypospadias*	
	Absent/abnormal testis	O-T DSD, MGD
5	*Cystoscopy*	
	Cavity in posterior urethra	46,XY DSD with retained vaginal anlagen

12.2 Inguinal Hernia

Failure of the processus vaginalis to obliterate, leading to inguinal hernia, is a common anomaly requiring surgery in infancy. Because of testicular descent, the frequency in males is about ten-fold higher than in females. In the latter, there is often a sliding hernia of peritoneum being pulled into the sac by pressure from the prolapsed bowel loops. As the attachment of the broad ligament to the lateral pelvic wall is close to the internal inguinal ring, the ovary (with adjacent fallopian tube) is commonly found in the hernial sac. The anatomy demonstrates that this is not a normal descent of the gonad, as seen in boys, as the ligament of the ovary, which is homologous with the cranial

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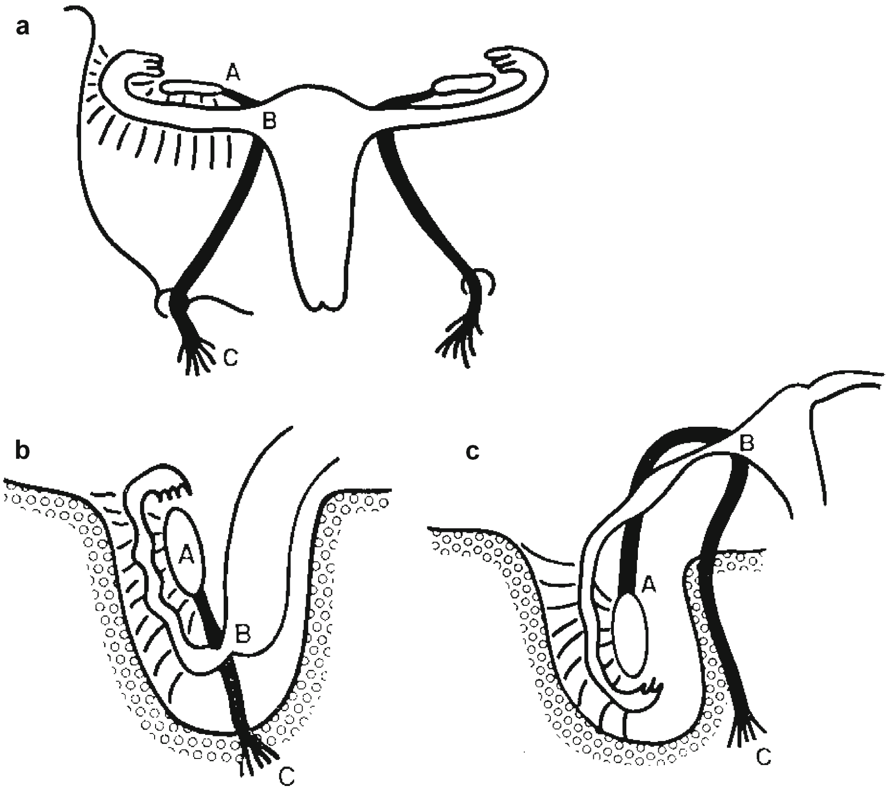

Fig. 12.1 (**a**) Schema showing normal anatomical arrangement of gubernaculum in a female, with proximal ligament of ovary attached to caudal pole of the ovary (*A*). The gubernaculum in the mid region (*B*) is attached to the Fallopian tube where it joins the uterus. The distal gubernaculum forms the round ligament, and ends just outside the inguinal canal (*C*). (**b**) If the ovary was normally descended in an inguinal hernia the gubernacular attachments (*A*–*C*) would all be in alignment as shown on the left. (**c**) However, when ovaries are found inside an inguinal hernia sac, the gubernacular attachments show that the peritoneum has been pulled into the sac, so that the cranial, not the caudal, pole of the ovary comes out first, as the gubernaculum is not attached directly to the lower sac (*A*–*C*), as it would be in a male

end of the gubernacular cord in males, passes back inside the inguinal canal to the uterine fundus. By contrast, in males, the gubernaculum attaches the caudal testis and epididymis directly to the bottom of the hernial sac (Fig. 12.1).

12.2.1 DSD Found at Herniotomy in Girls: CAIS

In 46,XY DSD caused by non-functional androgen receptors (CAIS), the child has an unambiguous female phenotype. In addition, because the Müllerian ducts are fully regressed, the vagina is slightly shorter than normal and blind-ending. The testes are the only internal genitalia, and they commonly reside inside the hernial sac in the inguinal region. The epididymis and vas deferens are absent in CAIS, as they require androgenic function for development. The gubernaculum (or genito-inguinal ligament) is more prominent than normal for the child's age, and attaches the testis directly to the caudal end of the hernial sac (Fig. 12.2a, b). The migration phase of the gubernaculum to the scrotum is absent as this requires androgens (Hutson 1985, 1986).

Are there any clues to the diagnosis before operation? In CAIS, the lack of functional androgen receptors means that the negative feedback on the hypothalamic-pituitary axis is absent, so that pituitary stimulation of the testes is increased. This leads to abnormal growth of the testes, which can be visibly larger than normal (Fig. 12.2a). Palpation of the enlarged gonad in the hernial sac may allow a pre-operative diagnosis of CAIS to be suspected. If CAIS is suspected on

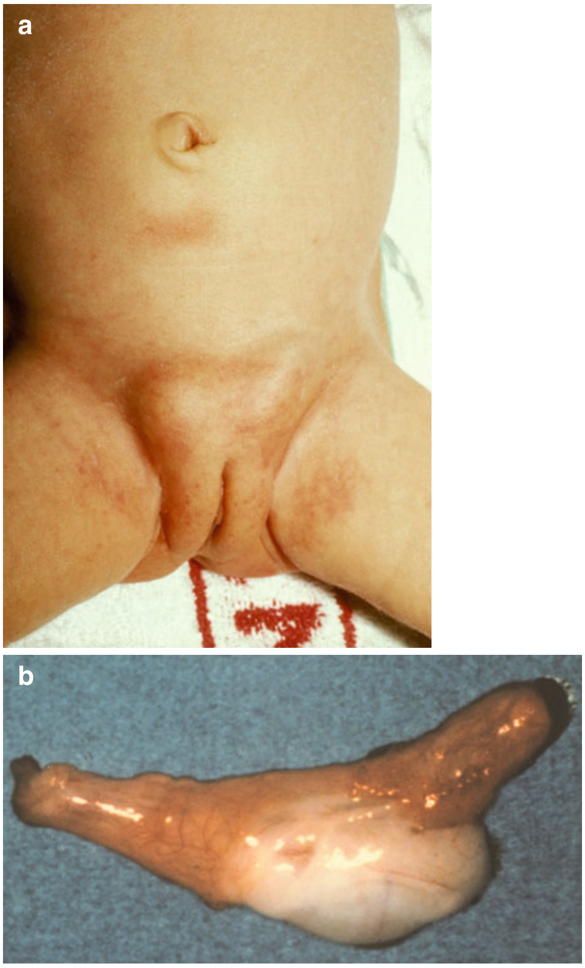

Fig. 12.2 (**a**) Inguinal hernia in a female infant with CAIS. The visible masses are the testes (which are enlarged because of lack of negative feedback on the hypothalamus) and the persisting enlarged swelling reaction of the gubernaculum. (**b**) Excised gonad in CAIS showing testis (with absent epididymis) and persistence of the swelling reaction in the gubernaculum

the operating table a rectal examination will confirm absence of the cervix, and passage of a blunt probe will demonstrate a short vagina (≈3 cm long rather than the normal ≈5 cm in a baby). Opening the hernial sac will confirm a testis without a normal adjacent epididymis but with a prominent, gelatinous gubernaculum, which is the persistent 'swelling reaction' of the first phase of testicular descent (androgens are needed to cause involution of the swelling reaction) (Fig. 12.2b).

Management depends on the timing of recognition of the DSD relative to the operation. When confronted with this unexpectedly, a sensible approach is to biopsy the gonads and replace them within the abdomen and complete the inguinal herniotomy as planned. Photographs of the gonads are extremely useful for documentation and providing a full explanation to the family. Gonadal excision is usually best left to a later date when the histological, hormonal and genetic studies have confirmed the diagnosis without doubt, particularly as current evidence suggests that orchidectomy can be safely delayed until after puberty has been completed. This is because the predicted cancer risk appears to be much lower than previously estimated. Hasty excision without all the evidence is a common trigger for litigation. Leaving the testes in situ allows normal induction of female puberty by aromatisation of the excessive androgens into oestrogens, while the risk of testicular tumour is extremely low until after puberty, and even then is not very high (Cassio 1990). Whatever age is elected for gonadectomy, this procedure would now be done by laparoscopy.

There is also evidence that inguinal hernias in girls may be more common in the MRKH syndrome (Oppelt et al. 2006; Khen-Dunlop et al. 2007).

12.2.2 DSD Found at Herniotomy in Boys

Several different anomalies of genital tract development can present first at inguinal herniotomy in an otherwise normal-looking boy (Table 12.1).

A common problem is inability of the surgeon to identify the vas deferens during isolation of the hernial sac, raising the question of whether the vas is either truly absent or it has been transected accidentally. A simple way to resolve this issue at open herniotomy is to stretch open the internal inguinal ring (which by definition is away from where the initial dissection of the spermatic cord has been done), the intra-abdominal vas deferens can then be identified easily if it is present. If the herniotomy is done laparoscopically, then the surgeon will notice that there is no vas deferens exiting through the internal inguinal ring.

Absence of the vas deferens is seen in two conditions: the Rokitansky sequence, and cystic fibrosis. In the Rokitansky sequence, the Wolffian duct migration to the embryonic cloaca is deficient, leading to absence of the vas deferens to a greater or lesser extent. If there was complete agenesis of the Wolffian duct, then the ipsilateral epididymis will also be absent. Müllerian duct migration to the cloaca stops at the same level, as there is no guidance without the Wolffian duct; but as the Müllerian ducts regress, their caudal deficiency is concealed. By contrast, the ipsilateral ureteric bud cannot form if the caudal Wolffian duct is missing, leading to agenesis of the ipsilateral kidney. Confirmation of the Rokitansky sequence can be obtained by renal ultrasound to show a single, contra-lateral kidney. During laparoscopy the surgeon may observe that the ipsilateral ureter is absent if the boy has the Rokitansky-sequence anomaly.

The second abnormality of the genitalia associated with unexpected absence of the vas deferens at inguinal herniotomy is a mutation of the CF gene (Sung and Hutson 2003). Bilateral congenital absence of the vas deferens (BCAVD) occurs in males carrying mutations in the CF gene, some of whom may have clinical features of cystic fibrosis but most appear otherwise completely normal, with no chronic lung disease or pancreatic enzyme deficiency. In these boys, the anomaly is always bilateral, and the renal ultrasound is normal (Sung and Hutson 2003).

Rare occurrences of DSD during herniotomy include the finding of an ovo-testis rather than a normal testis inside the hernial sac, or the presence of a fallopian tube and infantile uterus in a boy presumed to have simple cryptorchidism and inguinal hernia. The latter situation is one of the common presentations for persistent Müllerian duct syndrome (PMDS), which is described in detail in Chap. 7 and in the next section.

12.3 Cryptorchidism

Failed testicular descent is one of the common features of DSD, but in most boys it presents as an isolated anomaly in a baby with no other obvious anomaly. This is the rare presentation for PMDS, where there is an impalpable undescended testis (uni- or bilateral) in the presence of completely normal virilisation of the external genitalia. Where there is a palpable mass in the inguinal region it can be a unilateral cryptorchid testis with attached fallopian tube and infantile uterus, also known as 'hernia uteri inguinalis'. An alternative finding is that the inguinal mass turns out to be both testes within the tunica vaginalis along with uterus and tubes, which is one of the presentations of transverse testicular ectopia (Fig. 12.3). In these cases the gubernaculum is abnormally elongated so that the testes and internal genitalia ducts can be delivered easily right out of the abdominal wound in a way not possible in either normal males or females (Hutson et al. 1987). This abnormal mobility may also lead to torsion of the genital tracts with loss of both testes, a situation that is well-described in PMDS (Josso et al. 1993).

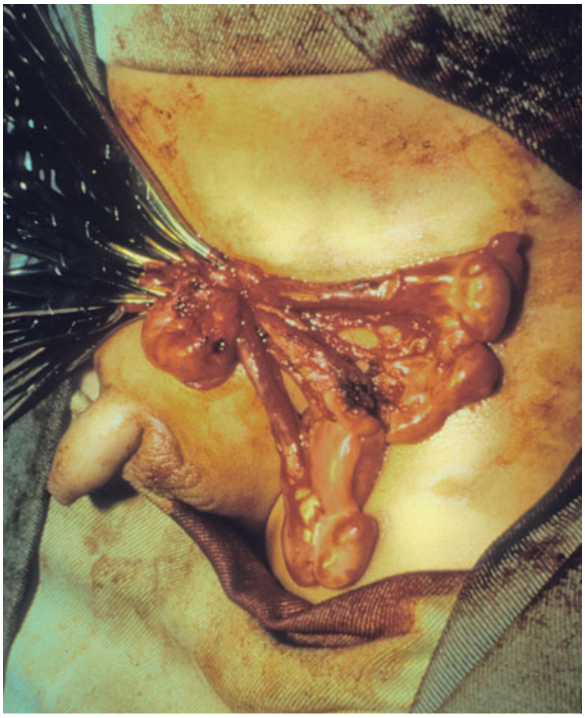

Fig. 12.3 Transverse testicular ectopia as part of persistent Müllerian duct syndrome (PMIDS), presenting with inguinal hernia (containing 2 testes, uterus and tubes) and cryptorchidism (Reproduced with permission from Hutson et al. (1987))

Where unilateral cryptorchidism is associated with hypospadias and bifid scrotum, there is a high possibility that the undescended gonad may be an ovo-testis or even an ovary (in ovo-testicular DSD), or an undifferentiated streak gonad (in 45,X/46,XY mixed gonadal dysgenesis). Once a DSD has been identified, then the overall management of the boy will need to embrace this. Nearly always the male gender will be retained, and the impalpable gonad and genital ducts (if present) will be managed accordingly.

12.4 DSD Found at Laparoscopy

Laparoscopic examination of the internal genitalia may be planned, as in such cases as 46,XY DSD with female phenotype with presumed streak or dysgenetic gonads (e.g. Swyer syndrome). Also in aneuploidy DSD with 45,X/46,XY Turner syndrome, there may be some sex chromosome mosaicism (Turner-Ullrich variant), where the steak ovaries need to be removed because of the risk of malignancy in Y-chromosomal cells.

In some patients, however, the abnormal internal genitalia may be found unexpectedly during surgery for other problems, such as diagnostic laparoscopy for abdominal pain. Gonadal anomalies in phenotypic girls include dysgenesis and streak gonads, while in boys there may be genital duct anomalies, such as absent vas deferens or presence of uterus/fallopian tube (PMDS). Genital duct anomalies are seen in females with the Rokitansky sequence, and as in boys, the surgeon should check to see if the ipsilateral ureter is missing, indicating Mayer-Rokitansky-Kuster-Hauser syndrome type 2.

One difficulty in infancy is that the uterus may be so small that it is easily missed on laparoscopy, particularly if the anatomy is distorted by other pathology. The child may be labelled as having uterine agenesis, when at puberty there is normal commencement of menses.

12.5 DSD Found with Hypospadias

Hypospadias is an abnormality of development of the penis, where the urethral meatus is on the ventral surface of the penis, rather than at the tip of the glans. Implicit in the name is the assumption that the baby is a boy, when in severe versions of ‘hypospadias’ the baby actually has a DSD. In the latter cases, there is abnormal development of the scrotum and/or testicular descent, which should alert the medical attendant that the baby is likely to have a more complex disorder than simple ‘hypospadias’ (Tong et al. 1996).

So when is ‘hypospadias’, not hypospadias, but a possible DSD? A useful rule of thumb for this is to only use ‘*hypospadias*’ as the initial diagnosis when the scrotum is normally fused and contains 2 testes. Any variant of scrotal fusion or gonadal descent in a baby with apparent hypospadias needs immediate referral and investigation for a DSD. Such babies may have gonadal dysgenesis or ovo-testicular DSD, or even CAH (Prader 4–5) (Scheffer et al. 1988).

If an older infant presents for management of their ‘hypospadias’, full investigation is required if the scrotum is bifid or both testes are not fully descended. Tests should include hormonal studies and karyotype, as well as a urogenital sinugram ± cystoscopy, to ensure there is no unrecognised vaginal remnant.

12.6 DSD Found at Cystoscopy

Occasionally, the diagnosis of DSD will not be made until cystoscopy is done in a baby with ‘hypospadias’ and bifid scrotum. The vaginal opening has several characteristic appearances. In some children, there is a visible opening somewhere between the bulb of the urethra and the site of the verumontanum in a normal male, through which a ureteric catheter or the cystoscope itself can be passed (Fig. 12.4). Another typical appearance is to find mucosal folds or polyps in the posterior urethra that look like seaweed floating underwater. This is the hymen, and the vaginal opening will always be found in the middle of these folds. The size of the retained vagina will depend on the degree of masculinisation in these children, who are most likely to have 46,XY DSD.

12.7 Precocious Puberty

One presentation for DSD that is not discovered incidentally at surgery is precocious puberty. The child presents with progressive signs of secondary sex characteristics as well as a recent growth spurt. The diagnosis may be hypothalamic, pituitary or gonadal disorders or tumours; but in the context of ambiguous external genitalia it is most commonly 46,XX DSD with CAH (See Chap. 22).

Occasionally, a DSD presents in a young girl with a pelvic mass, and only when the tumour is found to be a dysgerminoma is there realisation that the underlying diagnosis was a DSD with the gonad containing some Y-chromosome cells. Pre-operative hormone levels would have helped, and in the peri-pubertal girl recognition of her delayed puberty would also have helped.

12.8 Telling a Girl About Her DSD Diagnosis (with CAIS in Mind)

Over the past 20 years, clinicians dealing with children and adolescents with DSD have developed skills and improved attitudes with regard to the disclosure of medical information to parents. A number of information

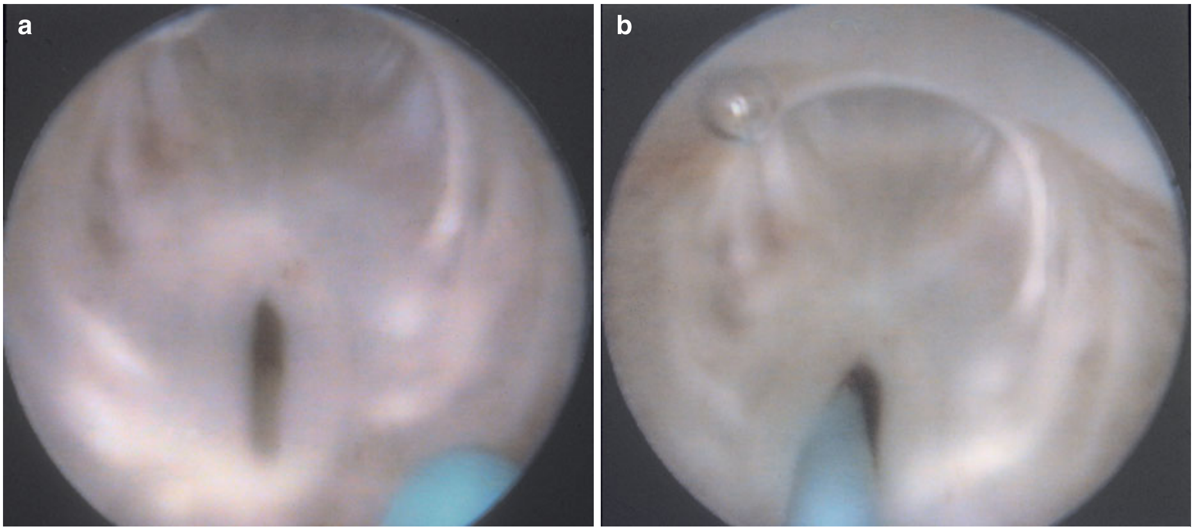

Fig. 12.4 (**a**) Cystoscopic appearance of persisting lower vagina opening into the posterior urethra. (**b**) Ureteric catheter passed through opening to measure length of retained vagina

booklets (Warne 1989; 1997) have been written to help with this. It is generally agreed that doctors have an obligation to disclose what they have learned from observation and investigation about children in their care to parents. The education of parents about complex and unfamiliar matters that are also potentially distressing requires the information to be presented in a form and manner that the parents, no matter what their education or cultural background might be, can understand. This is not a simple matter, as anyone with experience knows.

Disclosure of sensitive information to the child or adolescent patient is another challenge altogether. In the early 1990s and over a period of several years, a group of concerned doctors and mental health professionals at our hospital anguished about whether it was ethically justified to tell a girl that her chromosomes were 46,XY. The reason for the reluctance was fear that the girl would become depressed and harm herself. Indeed, some girls who prised the information out of their doctor during mid-adolescence or who discovered the information in some other way *did* become depressed and even suicidal.

A paper published in 1991 (Goodall 1991) suggested that the age of 12 years was a developmentally appropriate age at which girls of average intelligence and maturity could absorb and assimilate an explanation about a condition like complete androgen insensitivity syndrome (CAIS). Since then, we have followed that advice and have had no cause for regret. On the contrary, several girls who have now reached their early twenties have commented that for them, 12 was a good age to receive the information, that they had been able to understand it, and that they had not been unduly distressed at the time or later.

Each clinician will develop his or her own personal style of counselling. The following account is offered, not as a script that is to be read out, but as an example of the words and images that one clinician (GLW) has found helpful. The purpose of publishing it is to stimulate discussion that might lead to better ways of counselling and an improved outcome for young people with CAIS and similar conditions.

12.8.1 The Context

1. Parents have already been given information and have had a number of opportunities to discuss it with the child's doctor and other staff, for example, social worker.
2. They have been told that we think it is usually appropriate to begin disclosing the more sensitive information when the girl is about 12 years old.
3. They have had a chance to reflect on this and to begin introducing the subject at home.

4. We have had a chance to get to know the girl by seeing her with her parents on a number of occasions between the age of 8 and 12.
5. The girl would have always known that we would be giving her more information about her condition when she was older. She would also have been assured that any questions would be answered truthfully if she had any.
6. She would probably already have been started on oestrogen replacement therapy when she was 11 or 11.5 years old. She would have been told then that she needed to take these tablets because her body was not able to make enough of the hormone to help her start breast development on her own.
7. I would have asked the parents in advance to tell me what words they use at home for parts of the body, such as abdomen, female genital area, vagina, uterus.

12.8.2 The Setting

1. Outpatient clinic (or sometimes an office)
2. Not more than one observer or student in the room (who would have been asked to be as unobtrusive as possible)
3. Preferably both parents present (starting with the girl seated between them to maximize her sense of security)
4. I usually come out from behind the desk and sit on a chair positioned so that I can draw pictures on paper and the girl can see what I am drawing

12.8.3 Getting Started

1. Start from what she knows
2. That she comes to see me (a doctor) about a medical condition
3. That she was born with the condition and we have known about it for most of her life (or for… years)
4. That she is very healthy and can expect to stay that way
5. When she was a baby she had operations on the area of her vagina and her abdomen (use the words that the parents say the family uses) because things were not perfectly formed when she was born. That's why she has continued to come in and be seen by doctors

12.8.4 The Concept of Individual Variation

'Sometimes when babies are born, a small part of their body is found to be a little different from what most babies have. When this happens, the doctor talks to the baby's parents and helps them to decide what to do. Sometimes they decide that the baby would benefit from an operation to change that part of her body, to make it more normal.'

12.8.5 Informing the Young Person About Ways in Which She Was (And Perhaps Still Is) Different

'When you were born, a small part of your body was a bit different from how it should be. You probably know a little bit about this already. But your mother and father have been talking to us about you and they think that now is a good time for us to explain it to you, so you understand it a bit more. Are you happy for us to do that now?'

12.8.6 Disclosure About the Medical Condition

'Your mother has told you that when you were born, you had some lumps in the groin area (explain where that is) that looked a little bit different from other babies. When you were very small, you had an operation to take away the lumps and make everything look the way it should. At the same time, the doctors (or if appropriate, 'we') did some blood tests and X-rays to try to understand why you were born that way. What I am going to tell you now is what those tests showed'.

12.8.7 Introducing Fundamental Concepts About the Genetic Regulation of Sexual Differentiation

1. First I need to explain about how a baby grows and why no two people ever look the same. (Draw a picture of a cell).
2. If I take any small piece of tissue from a part of your body, such as a tiny piece of skin, and look at it under a powerful microscope, it is made up of individual

'cells' that are side by side and joined together. Cells are like tiny building blocks of the body.

3. Each cell looks a bit like a fried egg – it has a round bit in the middle like the yolk of an egg, called the nucleus, and an outside piece.
4. If we look at the nucleus with a microscope, we can see tiny pieces that look a bit like sticks. These are called chromosomes.
5. The chromosomes (or 'sticks') are made up of even smaller parts called genes. The genes are like little marks along the stick. Each gene (or mark on the stick) tells the body how it should work. You might have heard about the way Australian Aborigines used to communicate using message sticks. They would carve notches into a stick in such a way that the notches would convey a message to another Aborigine who had been taught how to read it. A certain pattern of notches might say, 'There's a dance on at our camp tomorrow night. Come on over'. The genes are a bit like that and a chromosome is like a giant message stick.
6. Every cell has chromosomes in the middle of it and every cell has an exact number of these chromosomes.
7. We get our chromosomes from our mother and father. When two people make a baby, half of the baby's chromosomes come from the mother and half come from the father. So for you, half of your chromosomes came from your mother and the other half came from your father. That is why you look like a mix of your mother and your father.
8. We've all got 46 chromosomes in every cell of our body. And these chromosomes hold about 30,000 genes (so that's like 30,000 grooves on 46 little sticks in every cell in our body!) It's amazing that they work perfectly as often as they do.
9. Every cell has two chromosomes that are there to decide if the baby will be a boy or a girl. We call these *sex chromosomes.* When doctors ask whether a baby is a boy or a girl, they are asking what sex the baby is. There are two kinds of sex chromosomes, a larger one called X (draw a picture) and a very small one called Y (another picture).
10. Most girls have two Xs and most boys have one X and one Y. But it doesn't have to be that way. There are girls who have only one X, or maybe three Xs and even some who have an X and a Y. There are also plenty of boys who have two Xs and a Y, or perhaps one X and two Ys. There is quite a bit of difference between people.

12.8.8 Going from the General to the Particular

1. As a matter of fact, although you are clearly a girl, you happen to have an X and a Y in your cells. The chromosomes are not the only things that control whether a baby is going to be born a boy or a girl. The way in which the genes are lined up on the chromosomes (in other words, how the grooves are arranged on the stick) is also very important. If they line up in a different way from the usual way, the message will have a different meaning. *Your* genes are lined up in a slightly different way from the average and that is why your body developed in a slightly different way.
2. We are not all the same inside our bodies (it would be boring if we were like peas in a pod). You probably know already that some children are born with a hole in the heart, or perhaps with one kidney instead of the usual two. We needed to have a look inside your body when you were very small because of the way your body appeared to be slightly different on the outside, and we did find some things inside that made you different. One important part of the body, called the uterus, or womb, was not there. We looked very hard to find it, but it had not grown in your body.
3. Other parts of the body, called ovaries, were also not there. When we looked for the ovaries, we couldn't find any, but instead we found parts called testes. Most people with testes are boys, but that's not always the case – some girls have them, too. Most people would be surprised to learn that.
4. When we thought about all these things together, we were able to understand why you were born the way you were. It is to do with the way your body reacts to your hormones.

12.8.9 General Information About Certain Hormones

You might have heard of hormones. Hormones are chemicals that travel around in your body and tell other parts what to do. 'Girl' hormones make breasts and hips grow so that the body becomes that of a woman.

'Boy' hormones usually make boys muscular, hairy and more fond of rough play. Everyone has some girl hormones and some boy hormones in them.

12.8.10 Going from the General to the Particular

When we looked at your hormones and how they work in you, we found that your body thinks that 'boy' hormones are 'girl' hormones. All girls have 'boy' hormones, but in you, they do not work as 'boy' hormones. We could give you as much 'boy' hormone as we liked and your body would think it was getting girl hormones and you would always continue to look like a girl.

12.8.11 Drawing the Association Between the Gene Change and the Hormonal Differences

We found that you are like this because one of the 30,000 genes in your body has changed (so one of the little grooves in one of the sticks is different). We don't know why this happened in you, but we know that genes can often change when babies are growing inside their mother's tummy. In fact, they say that every person on earth, including me and all of your friends, would have 5 or 6 changed genes that don't work exactly as they should. Usually it doesn't matter much, but some of the genes are more important than others. It just happens that the genes that changed in you caused some more important changes in your hormones, womb and ovaries.

12.8.12 Collating All of the Information

1. So what does all this mean for you?
2. Do you remember that earlier in this discussion, I said that when we looked for your ovaries, we could not find any, and that instead of ovaries, there were testes? When you were born, the doctors (or 'I' or 'we' as appropriate) explained to your parents that if the testes were left in your body, there could be problems. Testes do not belong inside the body and they develop harmful changes such as cancer if they are left inside. Your parents and the doctors (or 'I') decided that it would be best for you if the testes were taken out when you were still a baby. When you were young, you had an operation to take them out.
3. I know this is a lot of information to understand. The reason we want to explain this to you now is so that you understand why you need to take tablets.
4. The tablets are called oestrogen, which is the medical word for 'girl' or female hormones. Your body doesn't make enough oestrogen. That means that we will need to give you some extra oestrogen to start the process of puberty (explain).
5. That's why you have been prescribed oestrogen. Oestrogen will make your body develop into a woman's body like mother's. If we don't give you the extra hormones, you will stay as you are.
6. Do you remember how I said that you didn't have a womb? This means that you won't be having periods. This is because when a girl has a period, the bleeding comes from the womb, and you don't have a womb. That's a pretty big thing for you to take on board and we can talk about it some more when you have had time to think about it and talk to your mother and/or father about it.
7. Another thing is that you will have less hair on your body than other girls and your skin won't develop pimples. That's because the 'boy' hormones that all girls have cause them to develop pubic hair, hair under the arms, and sometimes, pimples. Your body doesn't respond to 'boy' hormones in the usual way so these things won't be happening to you. Lots of girls seem to be shaving off their pubic and underarm hair these days anyway, so you won't have to do that. In fact, this might be a great thing for you – not having to shave your legs or under your arms and not having to worry about pimples.
8. I have given you quite a lot to think about today. I'm sure you will have questions to ask when you have time to think about all that I have told you. Your mother, your father and I are happy to spend as much time as you need answering your questions to the best of our ability, and at any time.

12.8.13 Tell Her What You Have Told Her

The main things to remember for now are that:

1. Everyone has changes happen in their genes. Your gene changes have meant that your body is a little bit different from the usual.

2. One of the differences in your body is that you don't have a womb or ovaries. This means that you are not going to have periods.
3. Another difference in your body is that you don't make enough oestrogen on your own, so you will need to take oestrogen so that you develop pubertal changes. The oestrogens have other beneficial effects on your body, such as making your bones stronger.
4. The last main difference is that you won't grow pubic hair or hair under your arms, and you won't develop pimples when you go through puberty.

12.8.14 Give the Young Person Space to Ask Questions

1. Do you have any questions that you'd like to ask now?
2. I'd like to see you again soon to see how you are feeling about all of this and so that you can ask any questions you think of between now and then.

12.8.15 Comments

Any discussion of this sort has to be tailored to the occasion and reading from a prepared 'script' will not suffice. Readers will note that the issue of infertility is not addressed explicitly at the first discussion, which this is intended to be. Our experience is that it is best left for a subsequent meeting, by which time the girl and her parents have had time to reflect on the content of the first meeting and are ready to explore the implications more deeply. When talking about fertility, every effort to focus on the positive aspects and the possible sources of help for people to 'have a family' should be made. One former patient with complete AIS, for example, has become a mother, even though she had no ovaries and no uterus – she achieved it through surrogacy. No one likes to have all hope taken away from them and the truth is that we do not know what future scientific advances may have to offer.

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The Adolescent or Young Adult with DSD

13

John M. Hutson, Garry L. Warne, and Sonia R. Grover

13.1 Introduction

Most patients with DSD present at birth, in infancy or early childhood when genital anatomy is noted to be discordant with the sex of rearing. However, there is a small group where the presentation of a significant DSD is delayed until teenage or young adulthood. The conditions can be subdivided into two broad groups, depending on the sex of rearing (Tables 13.1 and 13.2). Co-ordinated team management during this crucial transition is important to ensure that the psychological as well as the physical issues are addressed (Liao et al. 2010) (see Chap. 24).

13.2 Phenotypic Females

There are numerous disorders of the hypothalamic-pituitary-gonadal axis that cause precocious puberty, but they are usually associated with completely normal female external genitalia. These conditions are not the subject of this chapter, but rather we focus on those disorders where sexual development is abnormal. The most important condition is CAH in a girl with minimal virilisation (Prader 1–2), where the minor genital differences went unnoticed at birth, and female gender was assigned and no treatment given.

13.2.1 Precocious Puberty

Severe salt-wasting forms of CAH usually present earlier with adrenal crisis, or more severe virilisation, so that delayed presentation of CAH in late childhood or early adolescence with precocious puberty is likely to be in the less severe non–salt-wasting forms.

13.2.2 Virilisation at Puberty

Many rare conditions can present with virilisation of a female at puberty. Usually they are manifestations of 46,XY DSD with severe under-virilisation prenatally, so that female sex of rearing occurred without any concerns about sexual development. Partial AIS has usually been diagnosed earlier in infancy, but minor genital virilisation may have gone unnoticed in some patients, who then develop some further clitoral enlargement at puberty.

Disorders of androgen synthesis quite often present with virilisation at puberty. Prenatally, the mutant enzyme was unable to produce enough androgen to trigger normal virilisation. At puberty, however, the growth of the testis is significant, and now the amount of testosterone produced is sufficient to trigger some virilisation, usually unwanted clitoromegally. A deficiency in 17β-hydroxysteroid dehydrogenase-3

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Table 13.1 Presentations of DSD at puberty/young adulthood in phenotypic females

Clinical scenario	Likely DSD
1. Precocious puberty	46, XX DSD with untreated CAH
2. Virilisation at puberty	Severe under-virilisation in 46,XY DSD with PAIS or androgen synthesis defects 5α RD2
3. Enlarging, tender swelling in groin	Inguinal testes enlarging in early adolescence in CAIS/severe PAIS/17βHSD3 Müllerian agenesis with inguinal hernias
4. Delayed puberty	(a) Gonadal dysgenesis
5. Primary amenorrhoea	Müllerian duct/vaginal agenesis
6. Deficient secondary sex characters	(a) TS (b) Deficient axillary/pubic hair with complete androgen insensitivity
7. Cyclical abdominal pains ± pelvic mass	Unilateral Müllerian duct agenesis/atresia (Rokitansky sequence)
8. Problems with sexual intercourse	Micro-perforate vaginal septum
9. Infertility	Müllerian agenesis Late-onset CAH
10. Secondary amenorrhoea	Mosaic TS

Table 13.2 DSD presenting in adolescence in phenotypic females

	Condition	Presentation
46,XY DSD	Complete AIS	Primary amenorrhoea No axillary/public hair
46,XY DSD	Partial AIS (with female phenotype)	Primary amenorrhoea Some axillary/pubic hair
46,XY DSD	Complete gonadal dysgenesis (Swyer)	Unexpected delayed puberty
46,XY DSD	Complete/partial testosterone synthesis defects (e.g.: 17α-OH deficiency)	Unexpected virilisation
45,X(46,XY)	Turner syndrome	Delayed puberty or delayed menarche (Presence of Y chromosome indicates risk of germ cell cancer – with potential for presentation with pelvic mass) Secondary amenorrhoea
46,XX DSD	Non-classical CAH 21-OH deficiency Or 11β-OH deficiency	Hirsuitism. Infertility
46,XX DSD	Müllerian agenesis	Primary amenorrhoea (In developing countries potential for presentation with primary infertility)

(17βHSD-3) (OMIM no. 264300) is the most common anomaly in testosterone biosynthesis that causes 46,XY DSD. Patients with 17βHSD-3 deficiency have a range of presentations, depending on the severity of the enzyme dysfunction. There may be clitoral enlargement, excess body hair, excess body odour or more severe virilisation with masculine body shape or even gender change to a male role (George et al. 2011).

One classic situation of female-to-male change at puberty is in 5α reductase-2 deficiency, although this will usually be already known in infancy because of ambiguous genitalia (Imperato-McGinley et al. 1974). At puberty, there is partial virilisation but usually there is no gynaecomastia and pubic, axillary and facial hair is reduced. The normal masculine hairline recession at the temple is absent. On rectal examination the prostate is deficient.

13.2.3 Groin Lump

Because the first phase of testicular descent is independent of androgenic function, those adolescent girls with 46,XY DSD caused by androgen blockade or deficiency may first present at puberty with enlargement of inguinal testes. At birth the testes are usually in the inguinal canal or just outside the external ring, and at puberty their growth may lead to tender masses palpable in the groin, which initially might be mistaken for an incarcerated hernia. Absence of other secondary sex characteristics or some minor enlargement of the clitoris would usually alert the clinician to the diagnosis (Ahmed et al. 2000).

A short vagina in association with the groin lumps may lead to the impression of a diagnosis of CAIS, but great caution needs to taken as there is a higher rate of inguinal hernias reported in girls with vaginal agenesis (Oppelt et al. 2006; Khen-Dunlop et al. 2007; Lortat-Jacob et al. 2007). Confirmation of these diagnoses with appropriate further testing is essential.

13.2.4 Delayed Puberty

Where there is complete gonadal dysgenesis with either XX or XY chromosomes (e.g. 46, XY DSD with complete gonadal dysgenesis [Swyer Syndrome]; 46, XX complete gonadal dysgenesis), the external phenotype is normal female and the internal genitalia are concordant, although the uterus remains infantile. In both circumstances, there is delayed onset of pubertal development with primary amenorrhoea. Ultrasonography will confirm the under-developed female genital tract and the gonads will be completely undescended and non-functional streaks. Care should be taken in interpreting the ultrasound reports in the presence of gonadal dysegenesis as the uterus will be a very small structure due to the lack of oestrogen stimulation. Ultrasonography, MRI and even laparoscopy findings have incorrectly reported 'no uterus' in these young women. Hormone levels will show absent oestradiol and increased plasma FSH and LH. Gonadectomy will be required, usually by laparoscopy for 46,XY complete gonadal dysgenesis.

In the 46,XX form of gonadal dysgenesis, there may be sensineural hearing loss present in about 10% of cases, and this is associated with an autosomal recessive inheritance, when it is known as Perrault syndrome. Distinction between premature ovarian insufficiency (POI) is not always clear if ovarian insufficiency or failure has occurred early. Investigation needs to cover other potential causes for POI including Fragile-X testing, and auto-antibodies looking for evidence of autoimmune origin for the ovarian failure.

13.2.5 Primary Amenorrhoea

Some patients with 46,XX chromosomes and normal ovaries on ultrasonography will have complete or partial agenesis of the Müllerian ducts and vagina. In its simplest form this may be an imperforate hymen that was not diagnosed with mucocolpos postnatally, and is now re-presenting with haematocolpos (see below – for cyclic abdominal pain).

In more complex forms, the vagina and/or uterus may be absent, so that there is no haematometrocolpos. In girls with these Müllerian anomalies, the remainder of pubertal development including axillary and pubic hair is normal.

It is not uncommon for the Müllerian agenesis to be the last of a series of previously diagnosed problems to be recognised, and a careful review for the other anomalies is often instructive. Renal anomalies are reported in up to 40% of girls, with unilateral renal agenesis making up half of these anomalies. Associated skeletal anomalies are also reported in 10%, (Creatsas 2009) and up to 10% of girls with vaginal agenesis will have evidence of having their Müllerian anomalies as part of the Klippel-Feil syndrome (Willemsen 1982) – the combination then being known as MURCS association.

The combination of cardiac anomalies and particular hand anomalies is Holt-Oram syndrome (HOS). The association between this and vaginal agenesis has been reported (Fakih et al. 1987; Ulrich et al. 2004). Likewise, the combination of cardiac, hand and oro-facial clefting is known as the velo-cardio-facial syndrome (VCFS) (Cheroki et al. 2006). For both of these conditions, there is evidence that there are recognised gene mutations. For HOS the mutations are in the gene coding for T-box transcription factor TBX5 located on chromosome 12q24 (Böhm et al. 2008) and for VCFS, the VCFS region of chromosome 22q11.1. Efforts to further delineate potential genetic mutations of Müllerian anomalies with these conditions, where there is a known genetic mutation by the searching for major deletions or duplications in these regions, has failed to show any abnormality (Hofstetter et al. 2008; Cheroki et al. 2006; Drummond et al. 2008; van Lingen et al. 1998).

The clinical distinction between CAIS and Müllerian agenesis, where both patients will have normal breast development, is the recognition of the scant pubic and axillary hair in the former. Nevertheless, the presence of other adolescent issues such as an eating disorder or participation in high-level athletics or sporting competition will impact on hypothalamic hormone production and peripheral adipose tissue conversion of testosterone to oestrogens. Thus, breast development, pubic hair and axillary hair may be influenced by factors other than the DSD and may make a clinical diagnosis difficult.

13.2.6 Secondary Sex Characteristics

Deficient secondary sex characteristics are seen in 45,X DSD with Turner syndrome and other causes of streak ovaries. Gonadal failure can be complete, but in many young women with TS and other causes of POI, the gonadal failure may be post-pubertal, yet premenarchal. Specific reduction in pubic and axillary hair is seen in 46,XY DSD with CAIS, and is the presenting complaint.

13.2.7 Cyclical Abdominal Pain

Müllerian duct development is normally associated with caudal fusion to create the uterus and vagina. Failure of this fusion produces a double vagina but normally no interruption in menstrual flow. However, in some circumstances the bifid genital tract is associated with ipsilateral absence of the kidney and lower ipsilateral vagina, and will present with an obstructed hemi-vagina at the onset of puberty. This is a characteristic presentation for the Rokitansky embryological anomaly known as the Máyer-Rokitansky-Kuster-Hauser (MKRH) syndrome (Acien et al. 2010; Takagi et al. 2010; Masse et al. 2009).

Transverse vaginal septa may consist of a thick membrane across the vagina, which obstructs menstrual outflow. The loss of a larger segment of the vagina is usually considered a vaginal atresia with these segments extending over 4–6 cm.

Cervical agenesis can occur in association with vaginal agenesis where the entire lower Mullerian tract is absent, but a uterus, or one or both uterine horns may be present, or alternatively, there can be an isolated absence of the cervix in the presence of a normal uterus and normal vagina. In the last decade, there have been several reports of successful anastamoses of the uterus without a cervix to the vagina (Fedele et al. 2008; Deffarges et al. 2001).

The terminology around rudimentary uterine horns is confusing, particularly now that uterine horns with an absent cervix are successfully being anastamosed and positive pregnancy outcomes reported (Deffarges et al. 2001). In general, rudimentary uterine horns represent varying degrees of Mullerian agenesis and can occur with or without a corresponding unicornuate uterus. The rudimentary horn can be either communicating or non-communicating (with the corresponding unicornuate uterus) and cavitated or non-cavitated, depending on whether the process of canalisation of the Müllerian structure has occurred. In the absence of canalisation, there is no cyclic pain and the detection may be incidental on imaging or at surgery, or alternatively, an ectopic pregnancy into this horn may occur (Jayasinghe et al. 2005).

The non-communicating cavitated horn usually leads to presentation with increasing dysmenorrhoea (where there is a corresponding unicornuate normal system). The cavitated horn without a corresponding unicornuate uterus will have its presentation as cyclic abdominal pain.

These conditions, where the uterus is present, but there is anomalous development of the vagina or cervix, are not generally considered DSDs, presumably as the diagnosis does not usually challenge the fertility potential of the young woman and there are no other features of atypical sex development. The definitions are still unclear as those women who have their rudimentary uterine horns removed, or their uterine horn in the setting of cervical agenesis removed, are in the same clinical predicament as those with uterine agenesis.

13.2.8 Problems with Sexual Intercourse

Some women with transverse septa have micro-perforations or tracts through the septum – and do not present with cyclic pain and a haematocolpos, but rather with pain or difficulty with sexual intercourse. Examination with a speculum reveals a smooth upper vagina with no evidence of a cervix – but with a history of regular menses. An ultrasound scan, particularly at the time of menstruation, will clarify the findings and help to define the thickness of the septum. Although other conditions with a slightly shorter vagina – such as vaginal agenesis or CAIS – may have symptoms associated with sexual activity, they are not usually the presenting symptoms for these DSDs.

13.2.9 Infertility

Some young women with vaginal and/or uterine agenesis will present with primary infertility – with their diagnosis of primary amenorrhoea having been ignored. This occurs most frequently in developing countries where marriage occurs in the mid teens and the issue of primary amenorrhoea has not been addressed. In this case, the vagina may be normal – due to sexual activity having resulted in the creation of the vagina with a pressure dilator effect.

In the young woman presenting with infertility, hirsuitism and oligomenorrhoea need to be considered for the diagnosis of late-onset CAH or non-classical CAH. There may be no other evidence of virilisation. A 17-OH progesterone will allow this diagnosis to be made.

13.2.10 Secondary Amenorrhoea

Gonadal failure related to TS may be delayed. This is more likely in young women with the mosaic form of TS or one of the iso-chromosome variations. Additionally, women with POI may present with secondary amenorrhoea associated with ovarian failure. High FSH and low oestrogens will be found. The uterine volume will reduce in size with increasing duration of the secondary hypo-oestrogenic state. A low MIS/AMH will also be present confirming the low or absent ovarian follicle reserve.

13.3 Males (Table 13.3)

13.3.1 Haematuria

Blood in the urine is caused by a range of urinary tract disorders, but rarely this may be the presentation for 46, XX DSD with CAH, where the degree of virilisation was so great the baby was raised as a boy. At puberty, which is often precocious, masculinisation is present with secondary short stature. Despite the high androgens the female internal genital tract persists (in the absence of MIS/AMH), and responds to oestrogens from the ovary. Menstruation then leads to cyclical haematuria until the diagnosis is made.

Table 13.3 Presentations of DSD at puberty/young adulthood in phenotypic males

Clinical scenario	Likely DSD
1. Cyclical haematuria	46,XX DSD CAH Prader 4–5 raised as male
2. Abdominal/pelvic mass with absent testis	Chromosomal DSD 45,X/46,XY MGD with retained streak gonad
3. Deficient/failed pubertal development	Gonadal dysgenesis Partial AIS Hypothalamic – pituitary axis disorders Klinefelter syndrome 47,XXY
4. Infertility	Anatomical anomalies of vas deferens

13.3.2 Abdominal/Pelvic Tumour

This is the presentation of 45,X/46, XY with mixed gonadal dysgenesis, where the streak gonad has been left in the abdomen, and then has become malignant. Although this seems an unlikely scenario, an intra-abdominal streak gonad may be missed if laparoscopy has not been performed, and an inguinal exploration reveals no testis in a boy with 'hypospadias' and one descended testis. In this case, it may have been assumed that the testis is 'vanishing', following perinatal torsion. Gonadoblastoma is the usual neoplasm in the dysgenetic gonad containing a Y-chromosomal cell line, and adolescence is a frequent time of presentation, although gonadoblastoma is sometimes already present in infancy (Cools et al. 2006).

13.3.3 Deficient Pubertal Development

Inadequate pubertal masculinisation is caused by a range of conditions, from XY gonadal dysgenesis and PAIS through to hypothalamic disorders and primary mixed chromosomal DSD (aneuploidy), such as 47,XXY Klinefelter syndrome.

13.3.4 Infertility

Some DSDs have no abnormal phenotype or disordered physiology in childhood, but present later in life with male infertility. It is not the intention to provide an exhaustive description here, but several conditions will be highlighted that relate to the vas deferens. In complete bilateral agenesis of the vas deferens (CBAVD), pubertal development is normal and the man may present to an infertility clinic because of inadequate ejaculate (Stern 1997). This disorder is now recognised to be caused by mutations in the cystic fibrosis gene (Δ508), which codes for a chloride channel protein in the cell membrane. These men have none of the other features of cystic fibrosis (CF), although boys with clinical CF all have atresia of the caudal epididymis and vas deferens (Sung and Hutson 2003).

The distal connections of the vas deferens into the ejaculatory duct and associated seminal vesicles are nearly always abnormal in patients with inadequate androgen production or insensitivity. As the Wolffian duct is developing between 8 and 12 weeks of gestation it must be exposed to adequate androgen levels to continue differentiating. Where the androgen effects are impaired, it is its distal end that undergoes involution, leaving a near-normal epididymis and proximal vas, but a blind-ending distal vas deferens. Often when there is concomitant deficiency of MIS/AMH, the caudal Müllerian duct is preserved and the distal vas deferens enters into a hypoplastic vaginal remnant (Ben-Meir and Hutson 2005). Normal maturation and transport of sperm is interrupted and the ‘plumbing’ abnormality is almost always related to infertility. Fortunately, assisted reproductive technology can bypass this anomaly in some patients who have viable spermatogonia in their testis or epididymis.

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Imaging in DSD

14

Murray Bartlett

14.1 Introduction

As well as clinical examination and genetic markers, imaging also has a very useful role in assessing the patient's sex. The radiologist can assist the DSD-management team in identifying the internal genital anatomy of the patient by assessing the presence or absence of a normal structure and by characterising any abnormal structure that may be present. Evaluating the presence or absence of the uterus or to characterise an abnormal adrenal gland are a few examples of structures that can be assessed.

Imaging of a patient with DSD may include more traditional types of investigations, such as genitography, to more advanced techniques like ultrasonography and MRI, although the most commonly used investigations at present are genitography supplemented by ultrasonography.

Clinical indications for imaging may include micropenis, clitoromegaly, hypospadias, cryptorchidism or obvious ambiguity.

The current consensus statement on DSD suggests that the first-line testing of newborns with ambiguous genitalia should include imaging (abdominal pelvic ultrasound study, genitogram) (Clayton et al. 2002; Houk et al. 2006; Nabhan and Lee 2007). These results are certainly available within 24 h and are often very helpful in the initial assessment.

14.2 Genitogram

Radiographic studies of the lower genito-urinary tract (genitography/sinugram) are important in the diagnosis and to assist in surgical planning. A genitogram is a study using fluoroscopy after catheterisation of the bladder and injection of contrast via the catheter to outline the bladder and vagina if present. The findings on these studies range from a normal micturating cysto-urethrogram (MCU)-like appearance (despite ambiguous genitalia clinically) to complex abnormal anatomy (Fig. 14.1a–c).

The sinugram/genitogram technique includes utilizing a sterile technique and ensuring that there are at least two catheters available prior to starting the procedure.

The radiologist should identify the number of perineal openings and then catheterise the urethra with a small catheter and fill the bladder with non-ionic contrast as per a routine MCU. This part of the examination will assess bladder position, communication with surrounding structures, fistulae, residual paramesonephric (Müllerian) or mesonephric (Wolffian) duct structures, vesico-ureteric reflux and possible uterine indentation on the bladder.

Often a urogenital sinus is identified, which is a common terminal channel for the anterior urethra and posterior vaginal pouch. This usually empties at the base of the phallus. This is suspected if there is a single perineal opening. A voiding study may outline all structures; otherwise, other techniques can be used after the cystogram portion to opacify the vagina and urogenital sinus.

Then, when the patient urinates the urethral length can be assessed, the presence or absence of a urogenital sinus and communication into the vagina can be determined.

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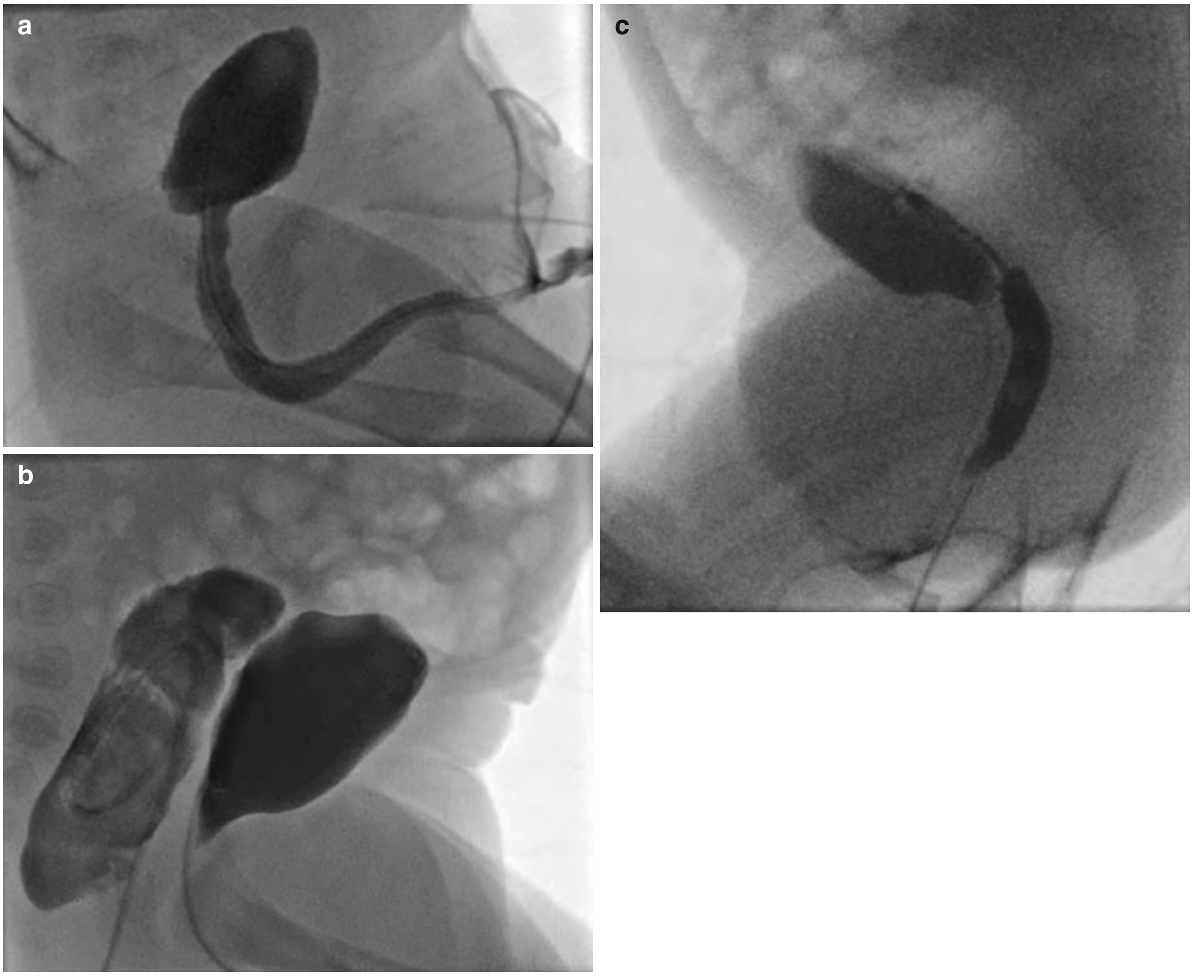

Fig. 14.1 (**a**) Normal Male Sinugram – The bladder is catheterised and during micturition there is no vaginal remnant demonstrated or vesicoureteric reflux. Normal male-type urethra opacified. (**b**) Normal Male Sinugram – In this case rectal contrast was also injected to outline the rectum and its relationship to the bladder. (**c**) Normal Female Sinugram – Contrast outlines the bladder anteriorly. Second catheter is in the vagina with contrast outlining the vaginal cavity. An endometrial cavity is also outlined. Note indentation of the uterus on the posterior aspect of the bladder

If the vagina is opacified, then the vaginal size can be documented and sometimes contrast demonstrated passing into the endometrial canal (Fig. 14.2a) or fallopian tubes (Fig. 14.2b). Evidence for cervical indentation on the vaginal cavity may also be observed.

If there is no urination or if the vagina has not filled, then there are other options to opacify the genital tract.

1. Place a second catheter and try to position this into the vagina and then instil contrast into the vagina to outline it (Fig. 14.3a).or
2. Withdraw the first catheter slowly while injecting contrast to opacify the vaginal cavity (Fig. 14.3b).

Antero-posterior (AP) and lateral films including long urethral view should be obtained.

The radiologist may need to perform a retrograde study if the catheter can only be advanced into the distal urethra by placing a catheter into the urethra and injecting while observing the contrast pass in a retrograde fashion through the urethra and fill the bladder and perhaps other structures.

The study may show a cervical impression on the vaginal cavity if a uterus is present and there is generally a uterine indentation on the bladder also (Fig. 14.4C). The cervical imprint may not be present if the vagina is under filled or there is a very small uterus.

Minor anomalies such as small Müllerian duct remnants to small vaginal remnants can be outlined (Figs. 14.3b, 14.4 and 14.5).

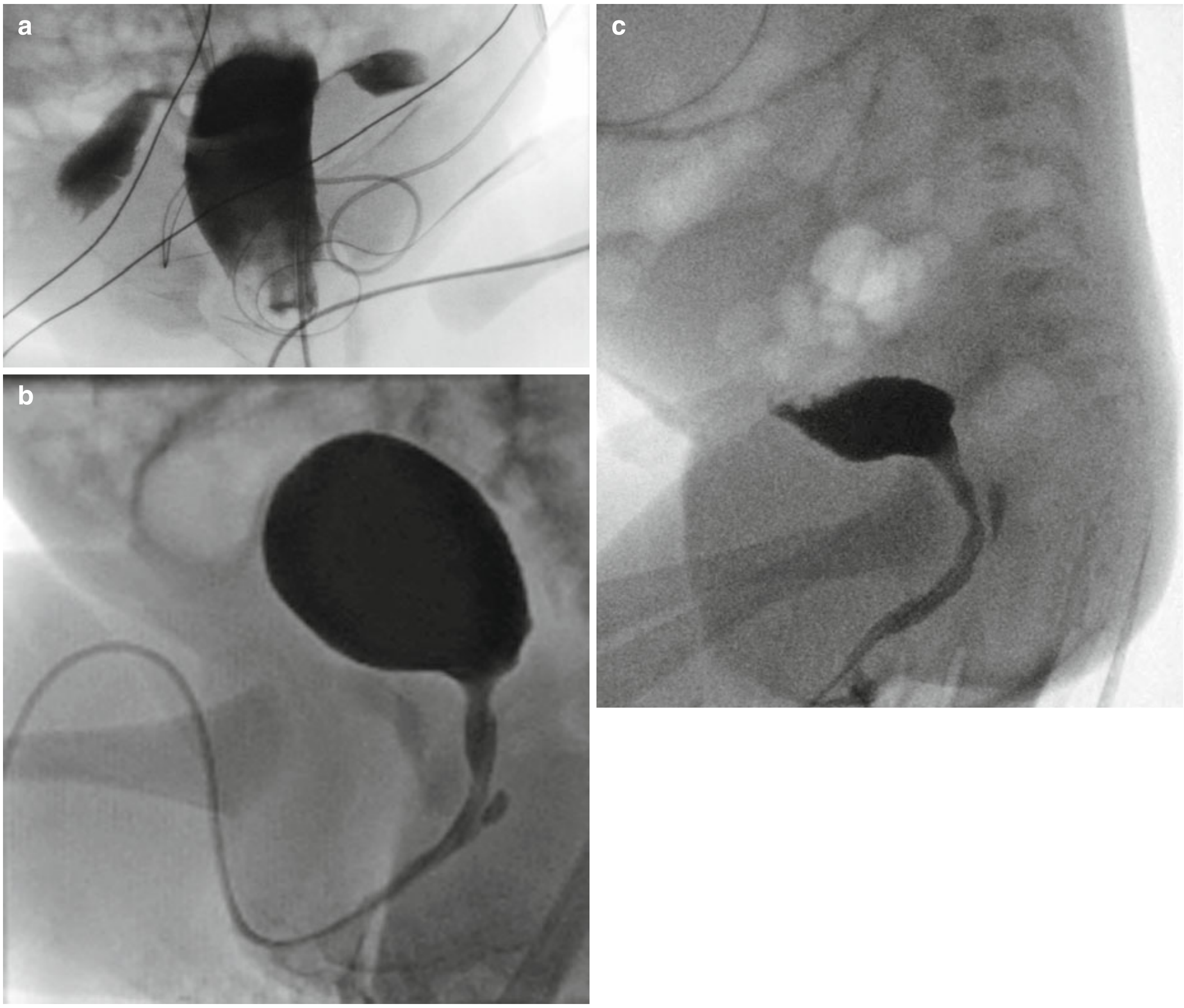

Fig. 14.2 Sinugram. (**a**) AP view demonstrates the vaginal cavity with spill of contrast into the fallopian tubes confirming their presence. (**b**) Oblique projection demonstrating a small Müllerian duct remnant. (**c**) Lateral projection demonstrates small vaginal remnant

The urogenital sinus may be very short or long. The length of the urogenital sinus and level of insertion of the vagina into the urogenital sinus are good indicators of the degree of virilisation. A metallic marker may be placed on the perineum to assist in estimating the urethral/urogenital sinus length (Fig. 14.3a); however, this does not assist with the true gender of the patient but may be of assistance in surgical planning.

The abdominal radiograph in these patients may also demonstrate additional findings and should be evaluated as well (Fig. 14.6), particularly, for non-hormonal causes of genital anomaly.

14.3 Ultrasonography

Ultrasound scanning is widely available and has the advantages of using no ionizing radiation as well as being reasonably quick and easy to perform.

The main role of an ultrasound scan is to identify normal structures, if present. These structures include the bladder, kidneys, adrenals and uterus, as well as the ovaries or testes and their location.

Trans-abdominal images should be obtained with transverse and sagittal orientation. A linear 9–13 MHz probe will produce excellent images of pelvic structures.

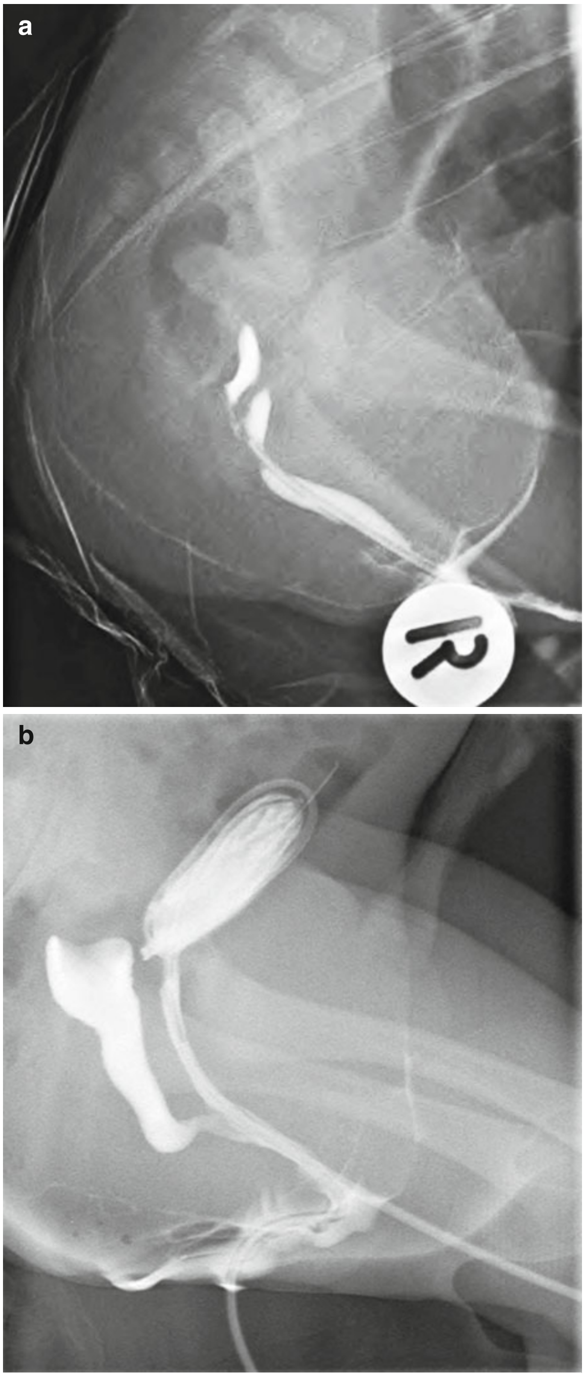

Fig. 14.3 (**a**) A metallic marker can be placed on the perineum to assist in outlining the perineal opening when assessment of urethral length is required. (**b**) Lateral projection demonstrates two catheters in situ – opacifying bladder, urogenital sinus and vagina. Note cervical indentation on the upper vagina

Ideally, the patient should be kept warm and wrapped to decrease movement and distress. As the parents are often present for the examination the sonographer or radiologist should limit their comments to the parents, perhaps suggesting the study is 'only one piece of the puzzle' and that the primary physician or surgeon looking after the patient will provide them with the results. A scan is done through a full bladder to assess the pelvic structures.

Hernanz-Schulman et al. (2002) demonstrated that in the neonatal period, ultrasound scanning has a sensitivity of 94% and specificity of 98% in detecting a uterus. The average length of (Blask et al. 1991) the uterus being 3.2 ± 0.5 cm, thickness 1.4 cm and volume 3.0 cc. An endometrial stripe was identified in 98%. Although allowing for more experienced sonographers to perform the study is thought to improve accuracy further.

As maternal and placental hormones are still present these lead to a relatively larger size of the neonatal uterus and ovaries, compared with later in infancy (Haber and Mayer 1994), and they are therefore relatively easy to demonstrate. Cervical length and width are often double in size compared with the fundus. Later on, during infancy, the proportion of cervix to uterine body changes to 1:1, with the uterine shape becoming tubular until just before puberty.

An echogenic endometrial stripe is also identified in the first few weeks and fluid may be seen in the endometrial cavity as a normal finding (Garel et al. 2001; Stranzinger and Strouse 2008) (Fig. 14.7a, b). A normal male ultrasound scan will demonstrate the bladder anteriorly and rectum posteriorly with no uterus in the axial plane (Fig. 14.8a).

Regarding the ovaries they have a mean volume of 1 cc. Follicles are generally visible; however sonography is unlikely to demonstrate the tubes (Banerjee et al. 1992; Cohen et al. 1992) (Fig. 14.7c).

In assessing for testis, a scan is made from the level of the kidneys to the scrotum or labia. These should be homogenous structures with no cysts or follicles (Figs. 14.8 and 14.9). Ultrasound scanning may also demonstrate an intra-abdominal testis; however, it is often not successful in detecting intra-abdominal testes due to their small size and overlying pelvic/abdominal structures (Figs. 14.10 and 14.11).

Perineal views can also be performed to demonstrate a view of the urethra (Fig. 14.8b).

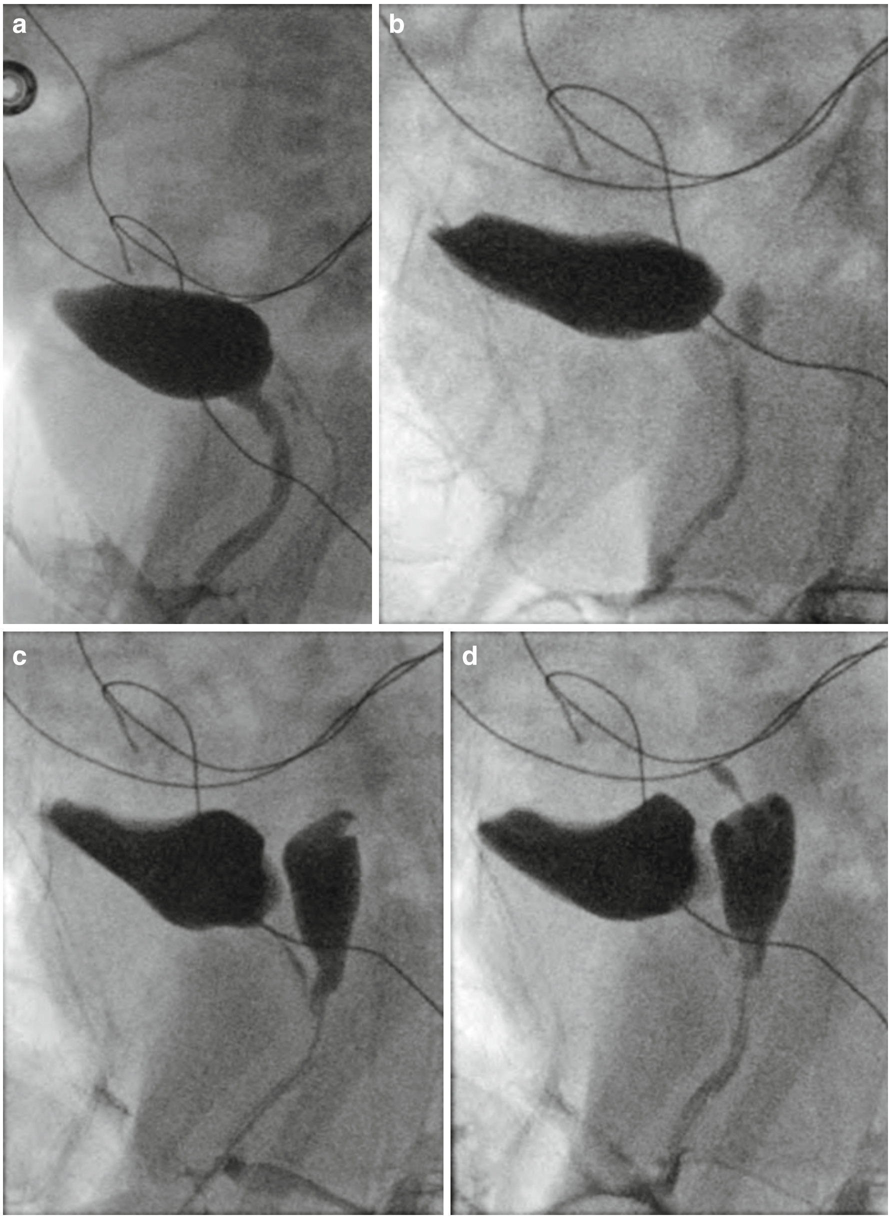

Fig. 14.4 Sinugram – series demonstrates initial filling of the bladder (**a**), small amount of contrast just entering the urogenital sinus (**b**). Later images reveal filling of a vaginal cavity (**c**) and subsequent contrast passing into the endometrial cavity of the uterus (**d**). Note cervical and uterine indentations

Ultrasonography is also useful to assess for associated renal anomalies such as a solitary kidney, obstruction, duplex kidney and crossed-fused renal ectopia (Ogilvy-Stuart and Brain 2004).

Additional structures such as paramesonephric (Mullerian) or mesonephric (Wolffian) duct remnants and hydrometrocolpos may also be encountered (Fig. 14.12). Most cases of hydrometrocolpos are associated with a urogenital sinus or cloacal malformation.

Common artefacts encountered include over-distension of the bladder, leading to a markedly inferiorly-displaced uterus, making identifying the whole organ difficult in the sagittal plane, with the axial plane being more successful in this situation. An empty bladder also makes identifying the uterus difficult. Identifying the rectum also assists in locating the uterus. In addition, bowel gas as well as bony structures may lead to artefacts.

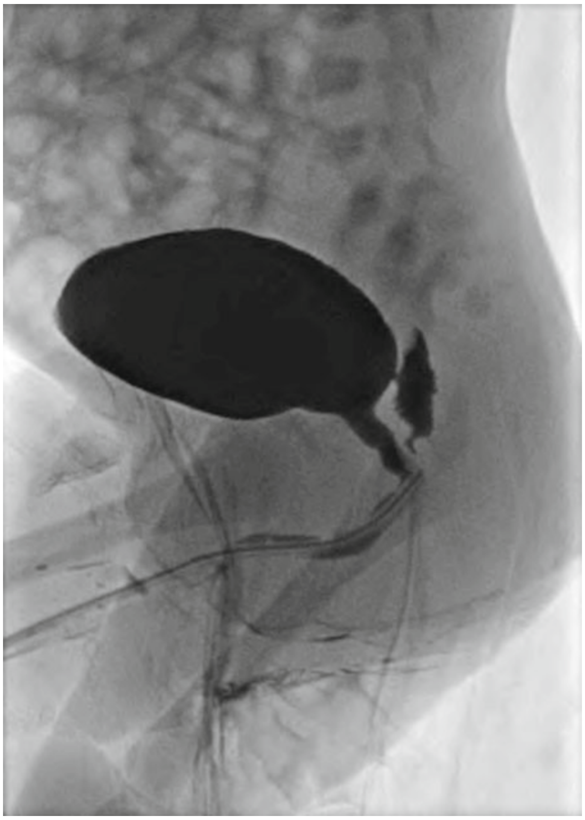

Fig. 14.5 Sinugram – demonstrates the catheter has been withdrawn out of the contrast filled bladder in order to opacify a small vaginal remnant

In ovo-testicular DSD, ultrasound scanning of the ovo-testes shows focal cystic areas among heterogeneous tissue with the cystic areas corresponding to ovarian tissue (Eberenz et al. 1991).

In complete androgen insensitivity syndrome (CAIS), ultrasonography demonstrates labia majora with testicles, which are often in the inguinal region or in the inguinal canal, as well as the absence of a uterus (Gambino et al. 1992) (Fig. 14.13).

14.3.1 Congenital Adrenal Hyperplasia (CAH)

Ultrasonography is an ideal imaging modality used to assess a possible congenital adrenal hyperplasia (CAH). Most commonly this is a 21-hydroxylase deficiency (90%) (Oppenheimer et al. 1983). As 75% of CAH have the salt-wasting variety, they are vulnerable to circulatory collapse if not diagnosed (Oppenheimer et al. 1983) early and, therefore ultrasound scanning can play an early role in assessing this.

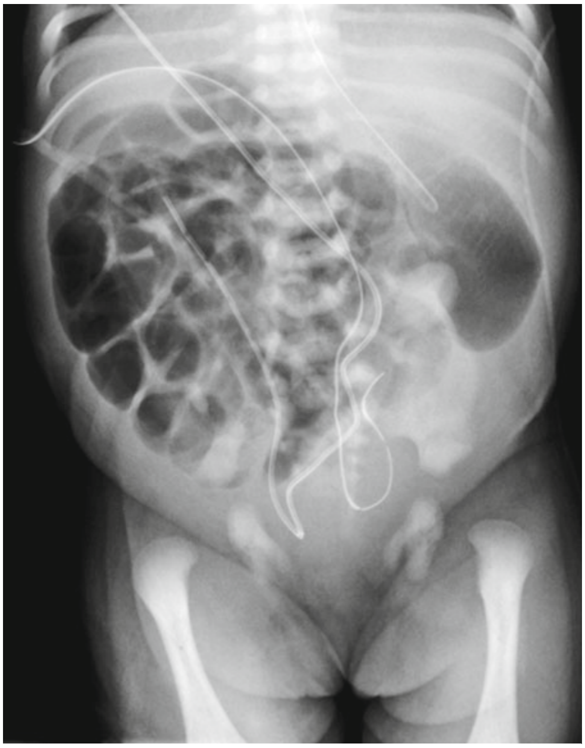

Fig. 14.6 Abdominal pelvic X-ray – patient has cloacal exstrophy demonstrating a wide symphysis pubis

In CAH, the sonographer will be able to identify a uterus and ovaries; however the adrenals will appear abnormal (Kutteh et al. 1995). A normal newborn's adrenals are routinely large relative to the older child's, and therefore easier to identify. Adrenal glands should be identified in all newborns. The normal adrenals resemble a triangle or inverted Y and they have a central echogenic stripe representing the medulla surrounded by a peripheral hypo-echoic rim of the cortex (Avni et al. 1993) (Fig. 14.14).

Both normal and abnormal adrenals have an echogenic medullary stripe. The exact size of the adrenal gland is difficult to measure due to the multi-planar nature of the gland. However, if the adrenals have a coiled appearance with a convoluted, cerebriform appearance, then this is highly specific for CAH (Oppenheimer et al. 1983; Al-Alwan et al. 1999; Sivit et al. 1991) (Fig. 14.15). These abnormal adrenal glands also have a generally bulky appearance compared to the normal (Hernanz-Schulman et al. 2002).

In untreated CAH, all adrenal glands will appear abnormal and after treatment return to normal size and shape; the axial plane being more successful in this situation. An empty bladder also makes identifying the

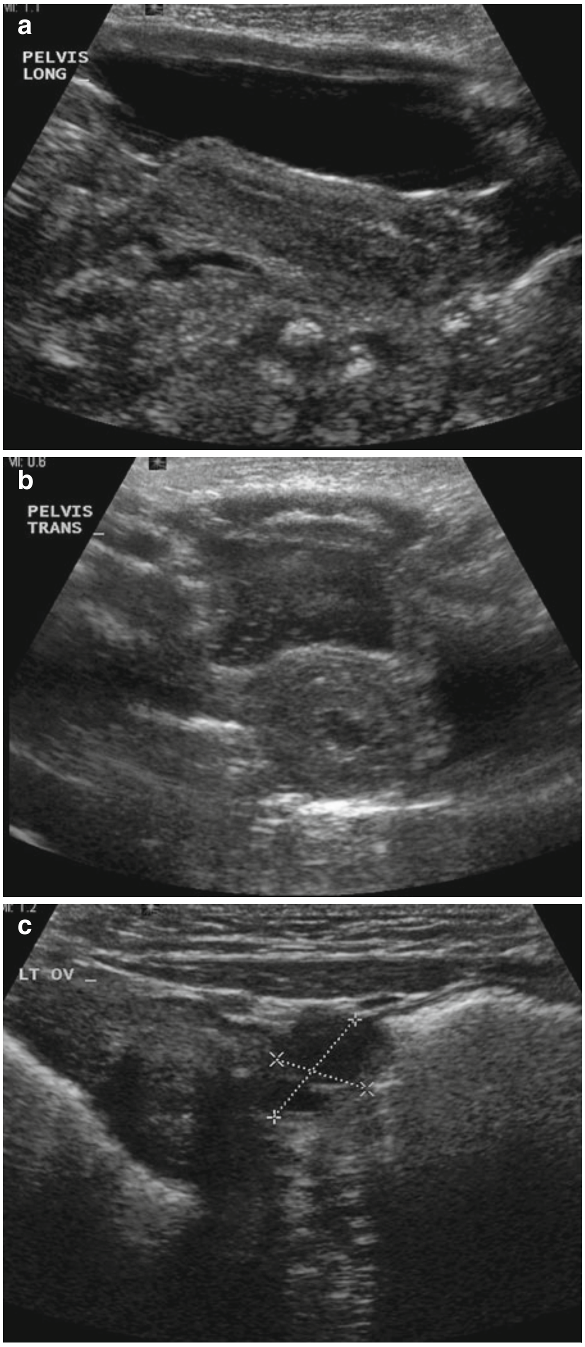

Fig. 14.7 Normal female pelvic ultrasound: (**a**) Sagittal view demonstrates the uterus. Note echogenic endometrial stripe and rectum posteriorly. (**b**) Transverse image through bladder and uterus. (**c**) Normal ovary with follicles identified

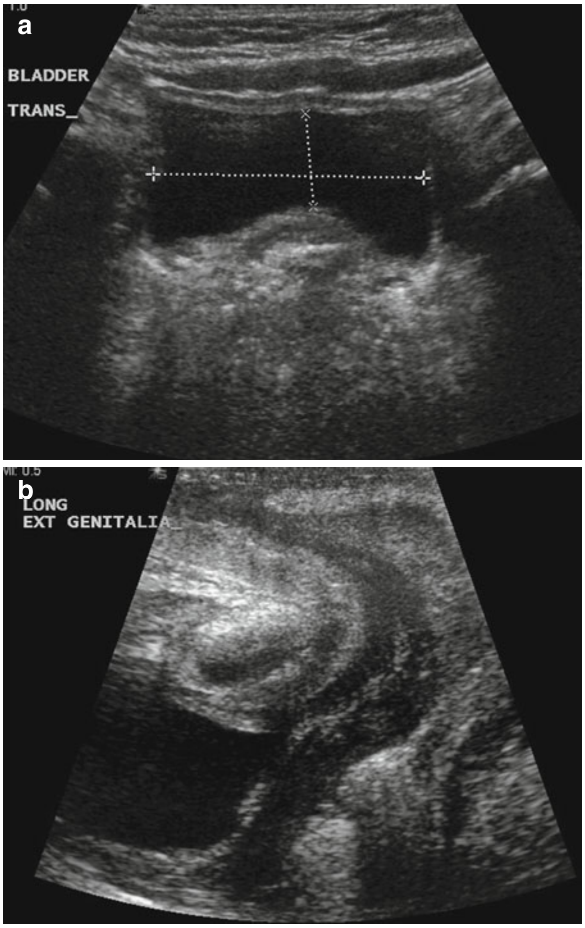

Fig. 14.8 Normal male pelvic ultrasound: (**a**) Transverse view – note bladder and rectum with no evidence of a uterus. (**b**) Perineal view demonstrates a long urethra. Note pubic symphysis

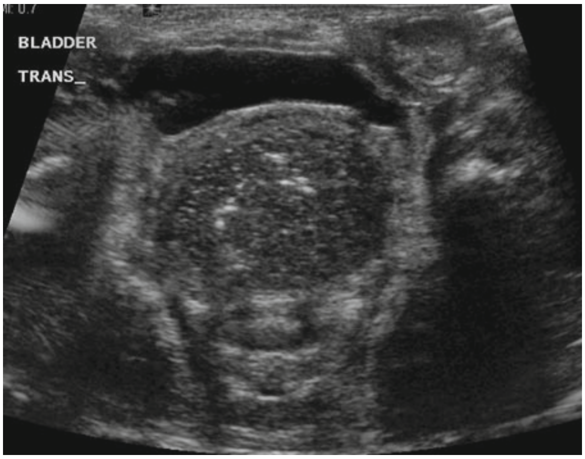

Fig. 14.9 Transverse ultrasound of male pelvis demonstrates bladder, distended rectum and no uterus. Note undescended testis with no evidence for follicles just to the left of the bladder

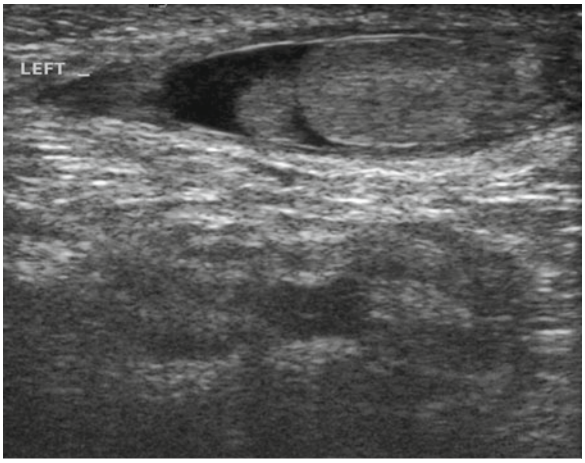

Fig. 14.10 Testicular ultrasound – normal testis in inguinal canal. Note absence of follicles and presence of mediastinum testis

uterus difficult. Identifying the rectum also assists in locating the uterus, although bowel gas as well as bony structures may lead to cause artefacts.

14.4 Magnetic Resonance Imaging (MRI)

In some European countries, MRI is routinely used to assess ambiguous genitalia in patients with DSD; however, elsewhere, it is usually a second-line test that may assist the clinician if the other imaging modalities are unhelpful.

Computerized tomography (CT) scanning is generally not used as the resolution of pelvic structures is limited. Sinugram and ultrasonography provide more accurate information than CT and, of course, there are also ionizing radiation considerations with CT. Incidental findings on CT performed for another reason such as for abdominal pain may be encountered later in life (Fig. 14.16).

The advantages of MRI include the ability to image in multiple planes without radiation, high contrast of the soft tissues and its relatively non-invasive scanning.

This modality can assess for one or more uteri, functional endometrial tissue, vaginal obstruction/duplication/absence, ovary depiction and to identify the kidneys; but it has a low sensitivity in identifying small rudimentary horns.

The technique will vary from institution to institution; however a general protocol will provide all the required information.

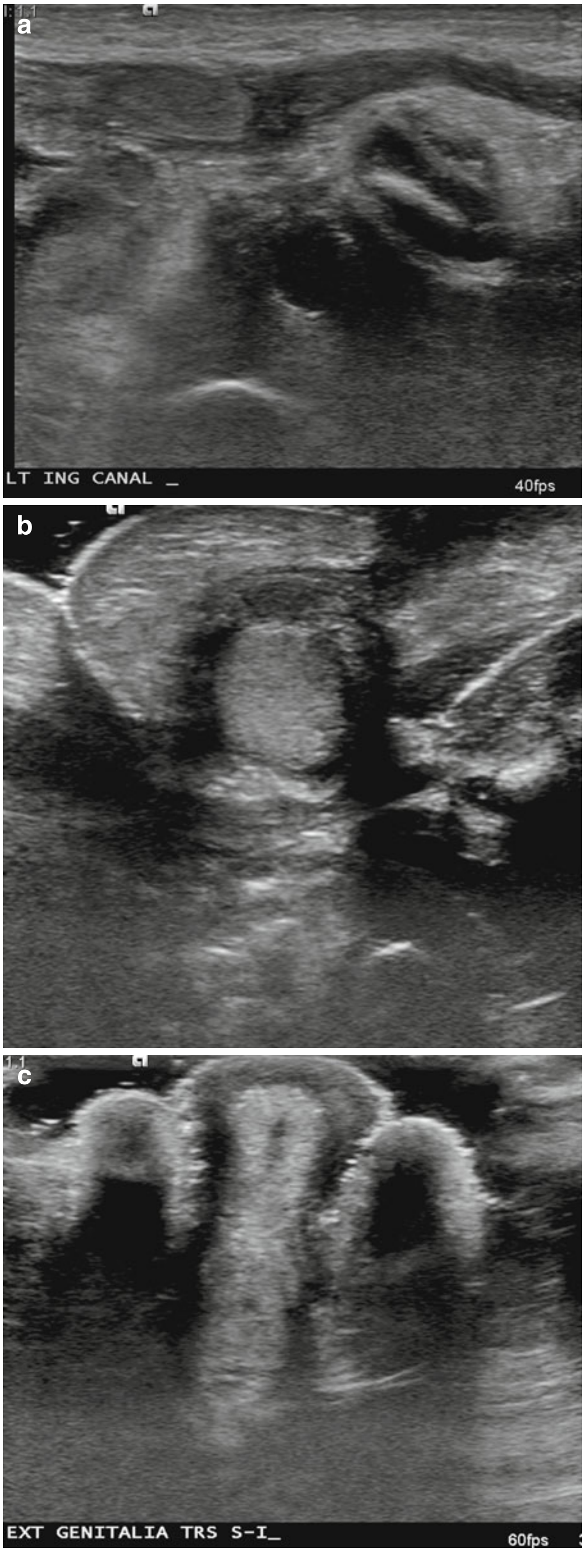

Fig. 14.11 (**a**) Pelvic ultrasound – sagittal image demonstrates an intra abdominal testis. (**b**) Ultrasound Image demonstrates testis within labio-scrotal folds. (**c**) Ultrasound Image – transverse view though ambiguous genitalia demonstrates labio-scrotal folds and a phallic structure but does not advance the true sex of the patient

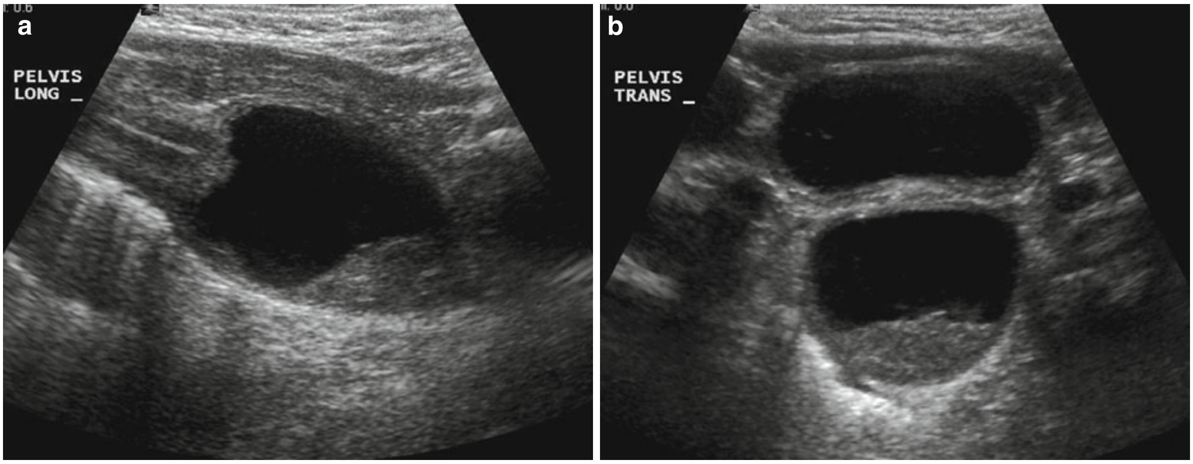

Fig. 14.12 Ultrasound images of hydrometrocolpos. (**a**) Sagittal view shows uterus/endometrium and haemorrhagic debris. (**b**) Transverse view of hydrometrocolpos

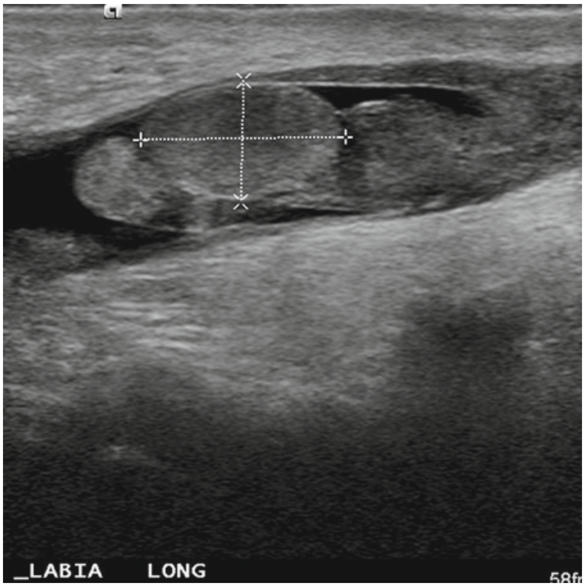

Fig. 14.13 Ultrasound in patient with CAIS. Note testis within patent processus vaginalis. These structures were contained in what was clinically thought to be labia

1. Phased array or surface coils to allow highest resolution.
2. Coronal T1- and T2-wide full view including kidneys and ovaries.
3. FSE T2 (sagittal) is excellent for anatomy of the uterus and vagina and also to determine their relationship to the rectum and bladder (Fig. 14.17).
4. The axial plane is used for ovaries, lower uterine segment and cervix.
5. The vagina is best seen on T2 axial slices (Hata et al. 1989).

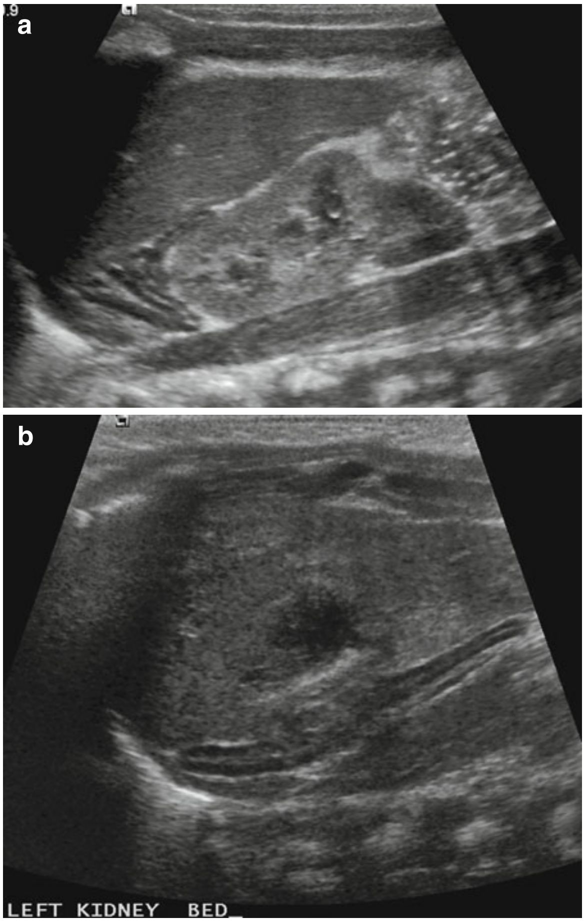

Fig. 14.14 Normal adrenal ultrasound: (**a**) Note hypoechoiec cortex and hyperechoeic medulla. Note the lack of a fine, coiled cerebriform appearance. (**b**) Ultrasound of renal bed demonstrates 'lying down adrenal' which is demonstrated with agenesis of the kidney

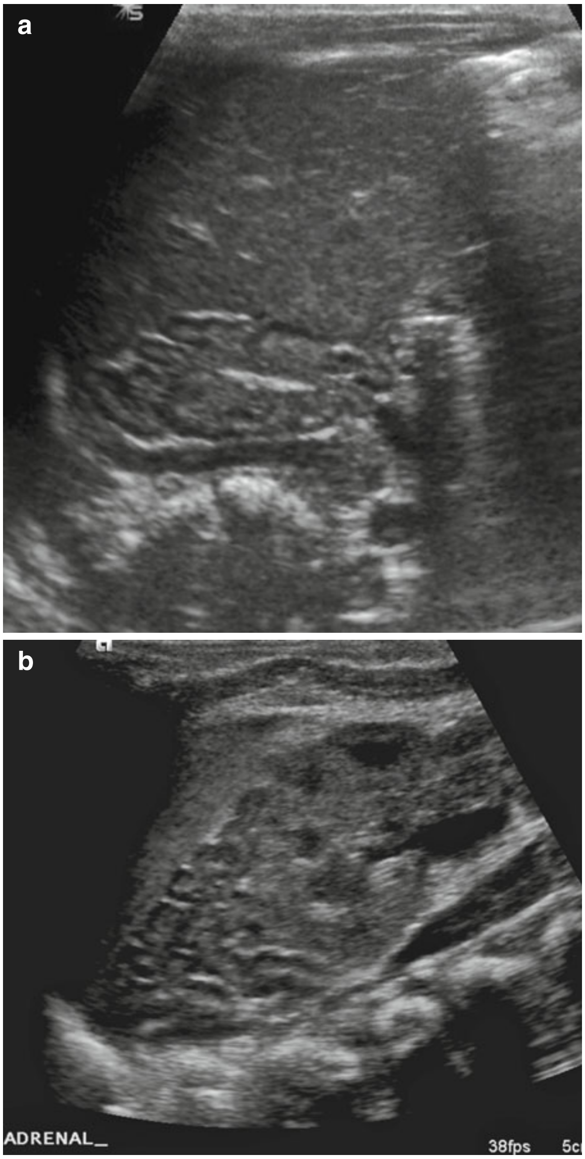

Fig. 14.15 Ultrasound suprarenal region in CAH: (**a**) Note enlarged appearance to the adrenal gland with increased number of gyrations giving a coiled, cerebriform appearance. (**b**) Transverse image demonstrates cerebriform appearance of CAH

In the neonatal period, there is oestrogen stimulation from the child's gonads, and therefore the fundus is usually larger than the cervix and there will be a high T2 signal in the endometrium. After 4–6 weeks, these features revert to the normal pre-pubertal appearance.

Vaginal epithelium in the newborn is a well-developed thick structure and also has a high signal on T2 (Cohen et al. 1993) (Fig. 14.18).

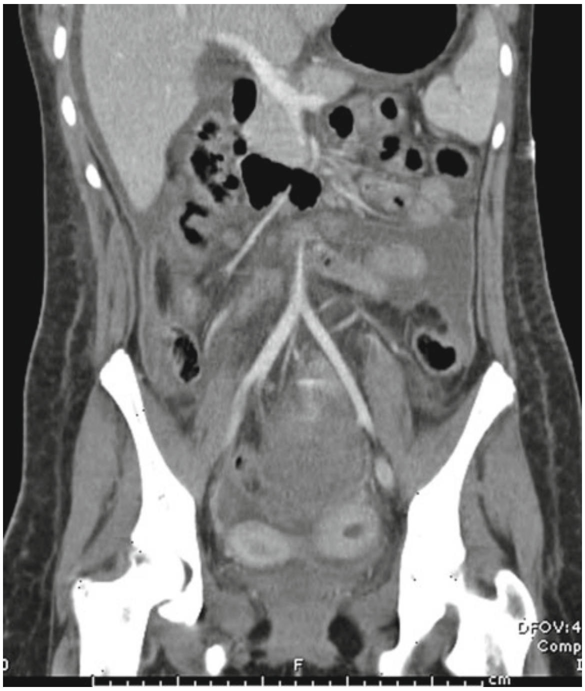

Fig. 14.16 Coronal CT demonstrates two uterine cavities in an adolescent

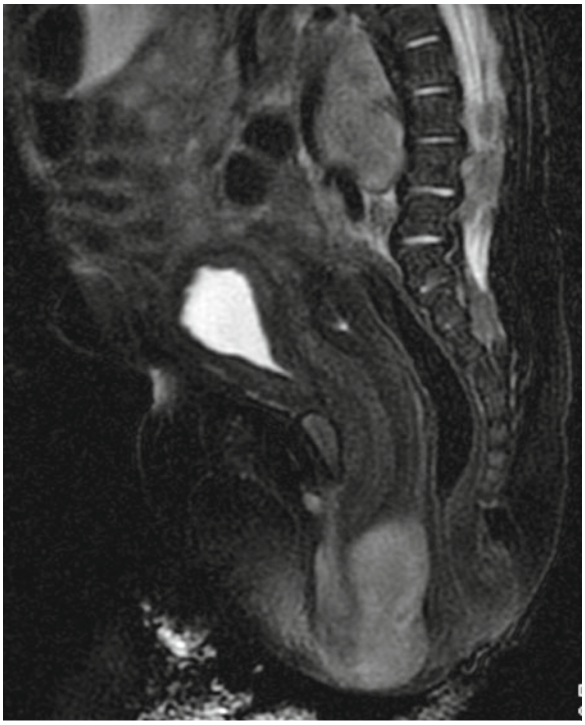

Fig. 14.17 MRI sagittal T2 image demonstrates bladder, uterus, rectum

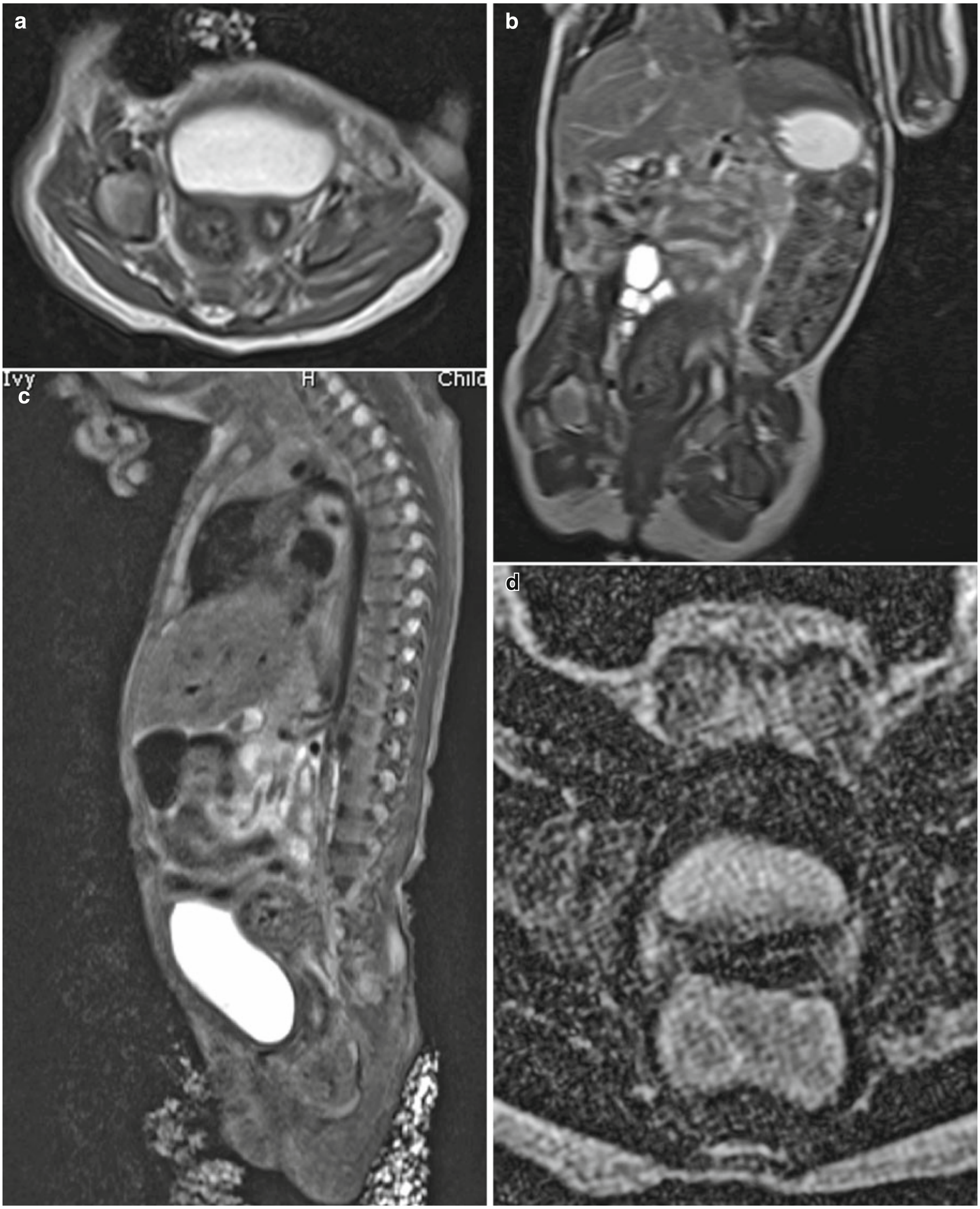

Fig. 14.18 MRI. (**a**) Transverse T2 image. (**b**) Coronal T2 – demonstrates uterus/endometrial cavity. (**c**) Sagittal T2 image showing normal anatomy. (**d**) Transverse T2 – inguinal gonads and uterus

Multi-planar images can confirm the absence of a uterus and demonstrate intra-abdominal or inguinal testis (Gambino et al. 1992).

Both testis and immature, non-cystic ovaries have intermediate signal on T1 and high signal on T2. Gonads often show an outer rim of medium intensity signal, which helps distinguish them from lymph nodes.

MRI may also demonstrate masculinised external genitalia and normal ovaries, tubes and uterus. Hydrometrocolpos can also be visualised (Gambino et al. 1992).

In 45,X/46,XY gonadal dysgenesis MRI may be useful to detect streak or dysgenetic gonads and characterise internal structure.

14.5 Imaging in Girls During Late Childhood and Early Adolescence

Appreciating the impact of oestrogens on the size of Müllerian structures is very important when attempting to interpret findings in a girl during childhood and early adolescence. Under the oestrogen influence, the Müllerian structures are usually readily identified, and where there is an endometrium present, a well-defined endometrial stripe will be visible. In the absence of oestrogen, the uterine structures are small and the endometrial strip may not be apparent at all.

Thus, an MRI and ultrasound scan performed in this older age group – particularly in girls presenting with primary amenorrhoea need careful interpretation. If the teenager is also pre-pubertal, the uterus will still be a very small structure on MRI and ultrasound, and can easily be missed or considered a rudimentary structure. Great care is needed in commenting on the absence of the uterus and vagina in a pre-pubertal girl when no oestrogen exposure has occurred. This includes girls with 46,XY gonadal dysgenesis, 46,XX gonadal dysgenesis or hypothalamic hypogonadism, who may all have incorrect reports of absent Müllerian structures.

Clarification of the Müllerian structures in girls with complex anomalies such as cloacal anomalies can also be challenging and often joint meetings with the radiologists and gynaecologists will be useful. In general, in the post-pubertal girl with a complex anomaly, presenting with pain, thick-walled pelvic (although potentially abdominal) structures, which are fluid (blood)-filled will be the uterus. If there is a relatively thinner-walled, blood-filled space below this, then this will be the vagina. The cervix may not be readily identifiable – apart from some potential hour-glass narrowing. The presence of a blood-filled space below the uterus defines the presence of a cervix. A fluid-filled structure, often snake-like in shape, with internal septations is likely to be a haematosalpinx. Additionally, a complex mass representing an ovary with endometriomas may also be present. In girls with cloacal anomalies, the presence of obstructed Müllerian components often does not correlate with the presence or absence of renal anomalies.

14.6 Conclusion

Imaging plays an important, early role in the assessment of the neonate with DSD causing ambiguous genitalia. Most commonly genitography (sinugram) and ultrasonography will be performed; however, MRI can play a role if other modalities have been unsuccessful in delineating structures.

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Ethical Principles for the Management of Children with Disorders of Sex Development: A Systematic Approach for Individual Cases

15

Lynn Gillam, Jacqueline K. Hewitt,
and Garry L. Warne

15.1 Introduction

Disorders of sex development (DSD) encompass a range of conditions, from mild misplacement of the urethral opening on the penis, to clitoral enlargement in a female child, truly ambiguous genitalia, or a complete discordance between anatomical and chromosomal sex (Hughes et al. 2006). It is known that ambiguous genitalia occur in 1 in 4,500 births; however, the true incidence of all forms of DSD is unknown (Hamerton et al. 1975; Sax 2002). For babies born with ambiguous genitalia, there may be a genuinely open question of what the sex of rearing should be and whether the baby 'actually is' male or female. These situations are emotionally and socially fraught, as well as technically challenging.

Selecting the best management for the various DSD can be complex. Difficult decisions must be made relating to sex of rearing, hormonal therapy and surgery. Surgery may be considered for a number of indications – to alter the appearance of the genitalia, to improve urogenital function or to reduce cancer risk. In addition to medical uncertainty regarding long-term outcomes of the various management options, there is a need to consider the family situation and social context, including prevailing views about gender, sexuality and fertility (see Chap. 19). Views on these matters have changed considerably over time in the Western world, and vary between cultures (see Chap. 21). Poor decision-making can lead to significant distress for the individual with DSD later in life (Schutzmann et al. 2009).

Decisions about infants with DSD are made today against a backdrop of dissatisfaction and anger of some adults with DSD, as evident in Dreger's edited collection (Dreger 1999) and concerns about the insufficient information and lack of opportunities for considered decision-making given to parents of infants with DSD (Chase 1998; Groveman 1998). The view has been put forward that no genital surgery should be performed until the child is old enough to understand the situation and make his or her own decision (Diamond 1998). There has also been considerable debate in the medical and ethics literature about the management of DSD, which addresses issues such as ethical failings of past medical practice, informed consent, the right of parents to make decisions about surgery for infants when the consequences are so far-reaching and fundamental to personal identity; and whether children should be surgically altered to suit the norms of societies, which happen to see gender only in stereotypical binary terms (Special Issue 1998; Spriggs and Savulescu 2006; Hester 2004; Karkazis 2008). In the context of these sorts of controversies, there have been moves in Australia (and also in Colombia) to have decision-making taken out of the hands of parents and doctors and placed with the law courts.

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Given this level of ethical and social complexity, great care and sensitivity is vital when making treatment decisions in individual cases. It is also vital, however, not to be paralysed by complexity. A decision pathway that takes account of complexity but does not get lost in it is needed. In this chapter, we propose a set of seven ethical principles on which to base treatment decisions for DSD, especially for decisions regarding type and timing of genital surgery for infants and young children. The first six principles were the basis for the resolution of the 5th World Congress on Family Law and Children's Rights in Halifax, in August 2009, on the medical and surgical management of infants and children with DSD (Halifax Resolutions 2009). The ethical principles were described in a presentation at the conference by one of the authors (Prof. Garry Warne), and were adopted as a resolution by a vote of the congress in the closing session.

The principles which we put forward are substantive rather than related to the process for decision-making. Our principles specify the considerations that ought to be taken into account by clinicians when making decisions, especially in the absence of clear medical evidence to direct management. They assume that conditions for good ethical decision-making, such as the procedural and process matters outlined by Wiesemann et al., are already in place (Wiesemann et al. 2009). These principles can be understood as describing in precise terms the nature of clinicians' basic ethical obligation, which is to act in the best interests of the child in this situation, taking into account the views and wishes of the parents. The first six principles relate specifically to infants, so are not formulated to include the views of the child with DSD. Decision-making for children who are able to have and express views, and may even have decisional competence themselves as mature minors, is much more ethically complicated, and we do not cover all the issues, but provide some general comments on the important principle of considering the views of the older child or young person.

15.2 Methodology

These ethical principles for management of infants with DSD were formulated by a process of dialogical analysis of clinician's reasoning in particular cases, in relation to established principles of bioethics (Beauchamp and Childress 2009). This was led by the ethicist in our team (LG), in systematic consultation with the clinicians (GW and JH). This process is a practical implementation of John Rawls' concept of reflective equilibrium as a method for building ethical theory (Rawls 1972). The crucial feature of reflective equilibrium is that it gives as much weight to individual ethical judgements in particular cases as it does to abstract moral theory, provided those judgements are made by those well-placed to decide. Ethical principles for a particular clinical situation, in Rawls' approach, are not simply derived from more general moral theory, but are built up by considering individual case judgements in constant reference to normative moral theory.

Using reflective equilibrium as a method means that we started from 'first principles', so to speak, rather than with the existing bioethics and sociology literature about DSD and the ethics of genital surgery. The analytic process focuses on judgements of expert clinicians in actual individual cases, and drawing inferences about generalisable principles that explain these judgements, and are consistent with moral theory at a relatively high level of abstraction. It does not focus on arguments put forward by ethicists, philosophers and others about the ethics of approaches to management and treatment of DSD, in general terms. Hence, this chapter does not refer directly to that literature. However, as would be expected, there are clear similarities between the principles proposed here and some of the arguments in the literature. The substance of each of our individual principles is not necessarily novel. What is novel is the process by which they were derived, and intended comprehensiveness as a set, which identifies all the relevant ethical considerations for decision-making in particular cases.

In the following sections, we set out the six principles that we identified as arising from the reflective equilibrium process, and give an account of their scope and theoretical ethical foundations. For each principle, we identify the specific clinical features that need to be taken into account, and provide key questions to aid in application of the principle. Application of principles, of course, requires clinicians to be aware of and use best-available current evidence about outcomes of various surgical procedures. Finally, we discuss the advantages of working with an articulated set of principles, rather than relying solely on the professional and ethical judgement of individual clinicians in their particular circumstances.

15.3 Proposed Ethical Principles for DSD

The primary ethical consideration in any form of medical treatment for children is the well-being (physical, psychological and social, both short and long term) of the child (Ross 1998). The other issue of major ethical importance is the parents' wishes. Generally, parents are entrusted with the responsibility of making medical decisions for their children in order to best promote their well-being in this broad sense (Pinnock and Crosthwaite 2005). However, when parents' wishes are likely to result in significant harm to a child (social or emotional or physical), consideration of the child's well-being takes precedence. This is sometimes known as the harm principle, and is well-established in ethics and law (Diekema 2004). In situations where the factors are complex and difficult to weigh up, and where future outcomes are difficult to predict, parents' wishes may be at variance with doctors' recommendations, without constituting clear harm to the child. In these situations, the parents' wishes should be respected (Dresser 2003; Jonas 2007). As children get older and become more able to understand their medical condition and its impacts, increasing ethical weight also attaches to the child's wishes and preferences (Ross 1998). These wishes and preferences may be in tension with both the parents' wishes, and medical views, making the situation even more ethically complex. However, in the context of DSD, significant decisions about sex of rearing and genital surgery have to be made while the child is very young, often during infancy (noting that a decision to delay surgery counts as one of the decisions that could be made, rather than a non-decision). For this reason, this chapter addresses the situation of infants and young children only.

For infants and young children with DSD, the fundamental ethical question relates to the potential harms a child is exposed to because of the particular DSD, which the child has, and what courses of action will adequately prevent or reduce these risks, allowing the child to have a good level of well-being over their lifetime. The following principles address that question by providing a specification in this particular context of the fundamental values of beneficence and non-maleficence (Beauchamp and Childress 2009).

The principles we propose are:

1. Minimising *physical risk* to child.
2. Minimising *psycho-social risk* to child.
3. Preserving potential for *fertility*.
4. Preserving or promoting capacity to have satisfying *sexual relations*.
5. Leaving *options open for the future*.
6. Respecting the *parents' wishes* and beliefs.
7. Consider the *views of older children and adolescents*.

15.4 Basis and Application of the Principles

It is clearly not always possible to fulfil every principle or right to the maximum degree. The nature of the DSD and the social environment into which the child has been born may make this impossible. It then becomes a matter of seeking to balance and weigh up the various principles in relation to the options available in the situation. The aim is to find the option that is the closest fit with the principles overall. This task requires clarity about the basis for each of principles and what they are intended to encompass.

15.4.1 Minimising Physical Risk to Child

Depending on which DSD the child has, there may be a range of risks to the child's physical well-being in the short term and long term. These typically include risks of malignancy, osteoporosis, adrenal crisis and urinary passage obstruction (Cools et al. 2006; Falhammar et al. 2007; Gozzi et al. 2005; Nabhan and Eugster 2007).

The questions to be asked in considering this ethical principle are:

1. How much harm would be done to the child if the risk eventuated? Would it mean loss of life, damage to an organ or body system, or less serious physical consequences? This is the magnitude aspect of risk.
2. To what extent could this harm or damage be corrected after it occurred?
3. How likely is it that the harm will occur? This is the probability aspect of risk.
4. What measures are available to reduce the risk?
5. How successful would the proposed measures be in reducing both the probability and magnitude of the risk, in comparison to other measures?
6. Do the risk-reduction measures carry their own risks or known negative consequences, and if so, are these less than the magnitude and probability of

the risks that the measures are meant to protect against?

The answers given to these questions will vary depending on the nature and severity of the condition at hand, and on the medical care that is available to the child in that particular setting. For example, the risks associated with not removing a gonad are lower if the gonad is palpable in the scrotum, rather in the abdominal cavity (Hughes et al. 2006). It is also possible that the answers will change in the future, as more evidence is acquired, and new techniques and drugs are developed.

15.4.2 Minimising Psycho-Social Risk to Child

The psycho-social risks to the child are somewhat more uniform across the different DSD, and typically include the following:

1. Risk of assigning the 'wrong' sex of rearing, meaning a gender that the child will later reject or feel uncomfortable with, potentially leading to gender dysphoria, depression or other mental health problems (Meyer-Bahlburg 2005).
2. Risk that child will not be accepted by parents in the chosen sex of rearing, leading to impaired bonding with associated negative consequences.
3. Risk of social or cultural disadvantage to child, for example, reduced opportunities for marriage or intimate relationships or reduced opportunity for meaningful employment and capacity to earn an income (Warne and Bhatia 2006).
4. Risk of social isolation, restrictions or difficulties, for example, caused by embarrassment or social stigma associated with having genitalia that do not match the gender in which the person lives.

All the questions relevant to physical risk, set out above, also apply to psycho-social risk. For all risks, consideration must be given to the magnitude and probability of the risk, and the extent to which it can successfully be reduced, either by the medical management options available, or by other types of support or intervention.

This process raises two difficulties. One is the present lack of solid evidence for making such assessments of risk. The second is the intangible nature of comparisons between physical and psycho-social risk. For example, it is not at all clear how to decide whether it is worse for a child to be at a risk of malignancy in the future, or at risk of distress in the future due to having their gonads removed as a child. This is where personal professional judgement and a good understanding of the family's social and cultural context are necessary. It is also a place where the parents' views might be given particular weight, as an authoritative source on the values held by their family or community. There is no evidence that can definitively adjudicate on this question, since it is ultimately a matter of the value that people place on the various different aspects of life.

15.4.3 Preserving Potential for Fertility

Fertility is listed here as a separate ethical consideration because it has both physical and psycho-social components. Infertility is both a physical dysfunction (which does not itself cause morbidity or mortality), and potentially a major psycho-social harm, depending on the importance attached to fertility by the individual concerned in their own social and cultural context. Fertility is a complex socially-mediated concept, and may relate to a number of different physical states, including:

1. Having ovaries or testes.
2. Having viable gametes, and hence having the possibility of having one's own genetic children, whether conceived naturally or by assisted reproductive technologies.
3. Having the physical capacity for one's gametes to produce pregnancy as a result of sexual intercourse, hence, being able to 'have children naturally'.
4. Being able to carry a pregnancy, whether or not the foetus has been produced by one's own gametes.

The key question is what courses of action offer the best chance of preserving the potential for fertility in a way that is likely to be meaningful for this person in adulthood. One ethical complexity likely to be raised by this principle is that courses of action that give the best chance of preserving fertility may bring with them higher risks of physical harm, such as malignancy – risks which could be removed, at the cost of losing the chance for fertility. Again, the relative weighting of these considerations cannot be scientifically determined, since they depend on subjective meanings and values. It is important to keep in mind that the subjective values that are relevant are those of the person with DSD, not those of the clinician. The difficulty is to try to foresee what these will be.

15.4.4 Preserving or Promoting Capacity to Have Satisfying Sexual Relations

Capacity for having satisfying sexual relations is arguably just one aspect of psycho-social well-being, which has already been dealt with above. It is listed separately here for two reasons: first, because it is more sensibly considered as a positive benefit to aim for, rather than as a risk to avoid; and secondly, because it can assume overwhelming importance in adulthood, becoming the foundation for all other aspects of psycho-social well-being, rather than one aspect among many (Cousineau and Domar 2007). Again, this is a complex matter, which involves values and interpretations, and not simply medical facts.

The key and contested issue is what counts as 'satisfying' in terms of sexual relations. Two obvious biomedical markers would be physical ability to engage in penetrative intercourse and physical ability to experience orgasm. If these physical capacities are preserved by the preservation of the relevant tissue, or enhanced by reconstructive surgery, this at least provides the physical basis for the psycho-social experience. For example, one reason for retaining all the tissue in an enlarged clitoris is that any surgery to reduce the size of the clitoris carries some risk of damaging sensory nerves and, hence, impairing the capacity for erotic response.

15.4.5 Leaving Options Open for the Future

Options for the future can be left open in a number of ways in relation to surgery for infants with DSD, including:

1. Not removing gonadal tissue even if it appears non-functional, to allow for the possibility that in the future, advances in medical technology may provide an option for fertility in those previously considered infertile.
2. Performing surgery in such a way that it leaves open the possibility of further surgery to change the assigned sex later on.
3. Delaying surgery which could be left until later in medical terms, so that the child or adolescent can have some input into decisions affecting their body.

Leaving options open for the future is an ethically important consideration for two reasons. First, it recognises the uncertainty inherent in decisions about sex of rearing and genital surgery. Knowing that things may not work out as expected or intended, the ethically responsible course is to take this into account when making decisions, and where possible allow scope for change of mind or change of the patient's circumstances or wishes. This is a strategy for meeting the ethical obligation to minimise harm to the patient and maximise benefit.

Secondly, leaving options open for the future provides a way to acknowledge and respect the rights of patients to participate in or make decisions about their treatment. Infants are completely incapable of making any decisions for themselves, so this right cannot be directly respected at the time, but the infant with DSD will grow up to be a young person with DSD, who has preferences, values and plans for their life. It is important to note, however, that leaving options open for the future is presented here as one ethical principle in a set of six. Our framework does not give it overriding status, or accord more weight to it than to the other principles. The ethical importance of leaving options open is to be considered alongside the principles of minimising physical risk, minimising psycho-social risk, preserving fertility and promoting the capacity for satisfying sexual relations. It may turn out to be a principle that cannot be fully adhered to in a decision, which must take account of multiple, potentially competing factors.

15.4.6 Respecting the Parents' Wishes and Beliefs

This principle is the most controversial, both in its wording and weighting. There are widely differing views on how much parents' wishes ought to be regarded as determinative. This difference of opinion can be seen in the final wording resolution of the 5th World Congress on Family Law and Children's Rights, where 'respect parents' wishes' was changed to 'consider parents' wishes'. Parents' wishes and beliefs are ethically significant for at least two reasons. First, they are closely implicated in the child's psycho-social well-being. How the child feels about himself or herself is very strongly influenced by the parents' attitudes and behaviours, and parent–child relationship is the basis of the child's overall well-being. In addition, the parents are the most knowledgeable about the family and social environment in which the child will be raised, and have the best sense of how others around the child will react to him or her, now and in the long-term. For example, in a culture that does not allow infertile females to marry and offers males more legal rights, freedom and privileges than females, a 46,XY child with ambiguous genitalia might be considered to have better chances of economic independence and a good quality of life if raised as a male than as an infertile female, even if the genitalia have a predominantly female appearance. Secondly, parents have a primary ethical responsibility to protect and promote their children's interests, and have a right to be allowed to carry out this responsibility. On this understanding, the parents' wishes matter because parents have a moral claim to be the decision-makers for the child by virtue of their parental role, and not just because they are likely to be well placed to make a good decision.

However, this right is not absolute. As mentioned earlier, the accepted foundational ethical principle of paediatric health care is that the child's interests are paramount, and that parents' decisions should be overridden if it is likely that they will cause significant harm to the child. By listing 'respect for parent's wishes' as an ethical principle alongside other ethical principles, these guidelines allow for the possibility that if the other ethical considerations point strongly enough against what the parents want, then it would be ethically appropriate to go against their wishes. Respecting parents' wishes does not necessarily mean doing whatever the parents want, but it always involves taking the parents' wishes (and the beliefs they are based on) seriously and according them moral weight. It also involves interacting in a respectful way with parents, even when their beliefs and values are radically different from those of the treating clinicians.

Our framing of 'respecting parents' wishes' as one of the 6 prima facie principles is potentially controversial. Some clinicians may hold that view that, in relation to DSD, parents' wishes are paramount and must always be followed. This may be based on an ethical belief, for example, that on matters of such personal importance as the gender and identity of their children, parents should have ultimate authority (even if they do not have absolute moral authority in other medical situations, such as life-saving blood transfusions for children of Jehovah's Witness parents). Alternatively, belief in parental primacy may be based on an empirically testable belief that, due to the nature of DSD, parents' decisions about treatment could never cause enough harm to the child to warrant overriding them. Clinicians who hold this second version will find that this set of ethical principles are compatible with their view, even if they do not endorse it. But clinicians who hold the first version, that parents wishes are paramount as a matter of principle, would disagree with these ethical principles, insofar as they do not give additional weighting or absolute primacy to parental wishes.

Others may take the opposite view, that parents' wishes are always secondary to considerations of the best interests of the child, or perhaps are not relevant at all. This position would amount to the claim that nothing significant is added to appropriate ethical deliberation by including the parents' wishes and beliefs. This would mean that everything that ought to considered in relation to the well-being and interests of the child can be fully covered by the other principles. This is a difficult position to maintain, since it seems to underestimate the extent to which the infant's future well-being, especially psycho-social well-being, depends on its relationship with its parents. Assigning a sex of rearing contrary to the parents' wishes, and making related decisions about surgery, has the potential for serious negative consequences for the child. For example, parents may strongly reject advice to raise a 46,XX child with ambiguous genitalia as female, if their perception is that the child is a boy and especially if they have told a wide range of friends and relatives that the baby is a boy. The difficulties for this child and family if doctors assign a female sex of rearing in the face of the parents' view are likely to be enormous.

15.4.7 Consider the Views of Children and Adolescents

The thoughts, feelings and wishes of the older child or young person with a DSD matter ethically for two reasons: promoting the psycho-social well-being of the child, and respecting the developing autonomy of the child or young person.

In relation to psycho-social well-being, much of the concern about psychosocial risk relates to how the child will be seen by others and by himself/herself: is the child distressed or embarrassed by their body, or by others' reactions to their body? If bodily changes are occurring due to puberty, how are they reacting to those changes? The child's thoughts and feelings about this are highly relevant to decisions about medical treatment even from quite a young age. Children also begin establishing a gender identity early on, and their feelings about their bodies are strongly shaped by what gender they perceive themselves to be. So, from about the age of 3 onwards (Slaby and Frey, 1975; Lutz and Ruble, 1995), children's thoughts and feelings are ethically relevant in making assessments of what would promote or hinder their psycho-social well-being, and whether a medical intervention (e.g. clitoral reduction surgery), would be ethically appropriate. This does not mean that children should be directly asked if they want surgery, nor that their views about surgery would be definitive; simply that their thoughts, feelings, ideas and preferences should be taken into account.

In relation to respect for developing autonomy, it is only later the children develop sufficient cognitive capacity to understand and consider for themselves the issues involved in medical treatment decisions. This capacity develops slowly over time, and comes at different ages in different children. No firm age cut-offs can be set and individual assessment is required. Once the child has started to develop this capacity, it is ethically appropriate to respect this developing capacity for autonomy by involving them in discussion or decision-making in ways appropriate to their developmental stage. The nature of this involvement and the ethical weight that should be accorded to child or young person's view (Buchanan Allen and Brock 1998) will increase over time. Some young people may develop a high level of decision-making before the age of 18, sufficient to be regarded as fully competent 'mature minors' who can make independent decisions and consent to treatment on their own behalf. This might occur by the age of 15 or 16, but again there is no defined age limit. Unless a child or young person is a mature minor, their wishes about medical treatment should not be taken as determinative, but should be taken seriously alongside other ethical considerations. The consent of a mature minor to medical treatment would be ethically definitive in theory, though parents' wishes at this stage are still very important. Disagreement between a mature minor and their parents about medical treatment such as genital surgery would be a significant ethical dilemma (Ross 1997) best managed with specialist clinical ethics consultation and legal advice.

15.5 Using Ethical Principles in Clinical Practice

These ethical principles can be used in a number of ways. Perhaps the most obvious use is by individual clinicians in their own thinking and decision-making about their patients. The principles could also be used to frame a discussion with parents, to help them understand their child's situation and the factors that need to be thought about when deciding on gender of rearing and any surgery (Gillam et al 2010; 2011). A third use is in a formal process of clinical ethics review. This is the practice that we have set in place at our own centre, Royal Children's Hospital, Melbourne. We are currently trialling a process where all new cases of DSD are routinely referred for review by the Clinical Ethics Response Group (CERG), which provides clinical ethics case consultation services for the hospital (Gold et al. 2011). The clinical ethics discussion takes place after a diagnosis has been made or confirmed, appropriate investigations and assessments have been completed and a management plan formulated in consultation with the parents, and patient, if old enough to participate (Fig. 15.1). The clinical ethics meeting is attended by the multi-disciplinary treating team, and members of the CERG, including the clinical ethicist and others trained in ethics. At the meeting, a discussion guide based on the principles set out in this chapter is used (Fig. 15.2) both to give some structure to the discussion, and to make sure that all ethically relevant aspects are fully considered. This process is organised so that there is minimal or no delay for the parents and patient. Ideally, CERG is notified when a patient first presents, some days to weeks in advance of time when a management plan will be available to discuss. In any case, the CERG is able to convene at 24–48 h notice. The process is not bureaucratic in the way that research ethics is: there is no application form, and lengthy documentation is not required. Clinicians complete a short proforma referral, which asks for the same information that would normally be provided when making a referral to consultant for specialist clinical advice (Fig. 15.3). In cases considered so far, the clinical ethics review process has not identified outstanding ethical concerns with the management proposed by the treating team. There is a process in place to deal with a situation, where ethical concerns are raised and cannot be resolved at that meeting. This involves a higher level of ethical review within the hospital, and possible

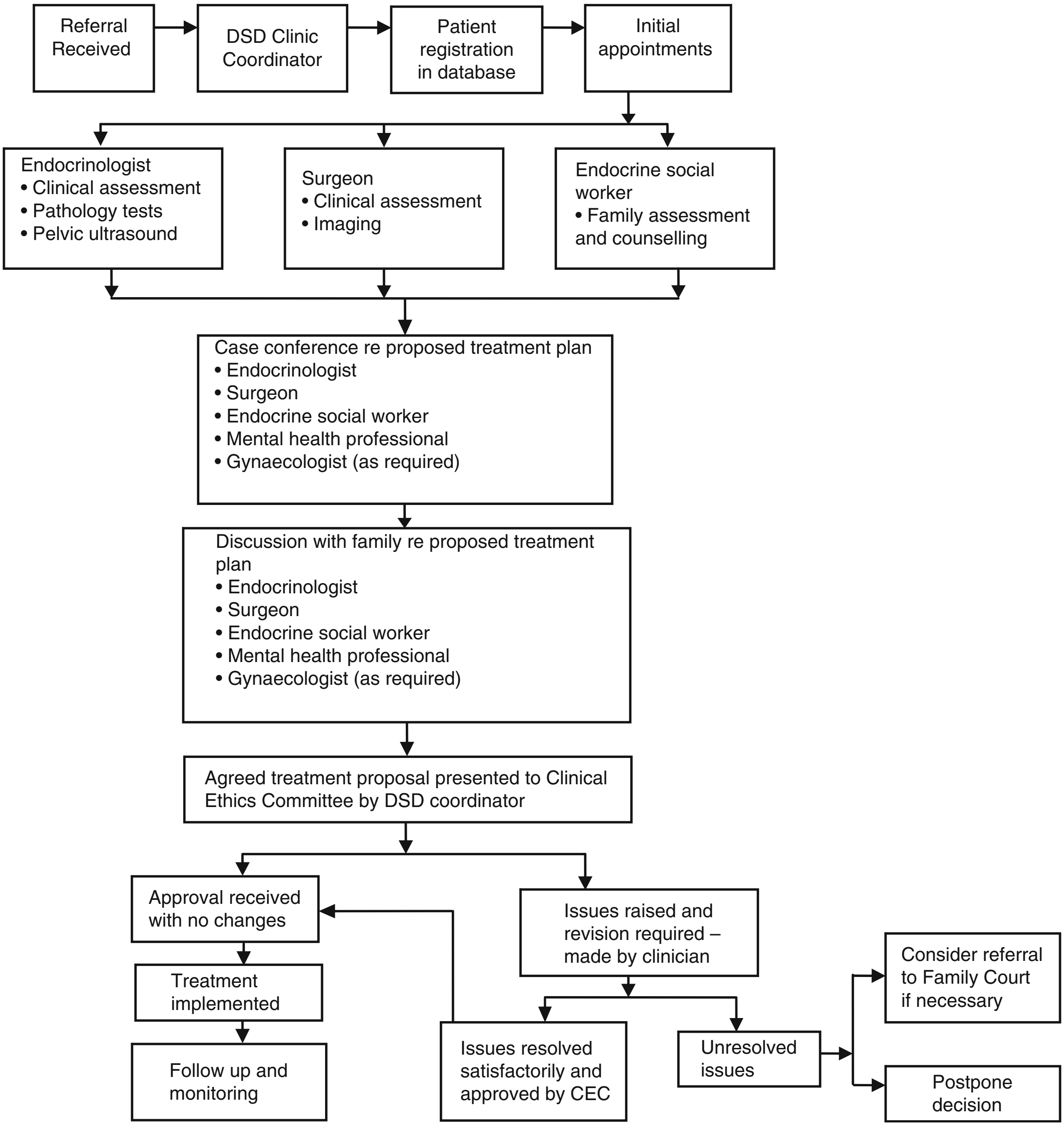
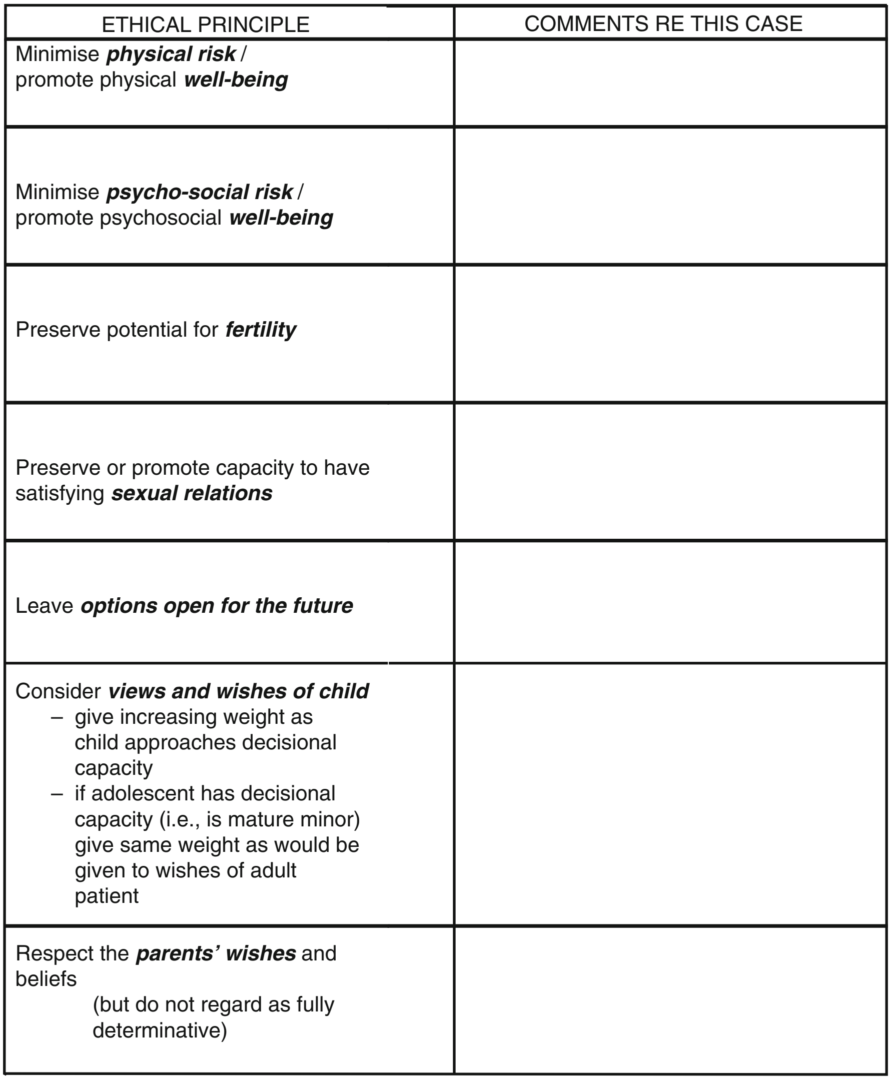

Referral Received
DSD Clinic Coordinator
Patient registration in database
Initial appointments
Endocrinologist
• Clinical assessment
• Pathology tests
• Pelvic ultrasound
Surgeon
• Clinical assessment
• Imaging
Endocrine social worker
• Family assessment and counselling
Case conference re proposed treatment plan
• Endocrinologist
• Surgeon
• Endocrine social worker
• Mental health professional
• Gynaecologist (as required)
Discussion with family re proposed treatment plan
• Endocrinologist
• Surgeon
• Endocrine social worker
• Mental health professional
• Gynaecologist (as required)
Agreed treatment proposal presented to Clinical Ethics Committee by DSD coordinator
Approval received with no changes
Treatment implemented
Follow up and monitoring
Issues raised and revision required – made by clinician
Issues resolved satisfactorily and approved by CEC
Unresolved issues
Consider referral to Family Court if necessary
Postpone decision

Fig. 15.1 Pathway for clinical ethics review of proposed treatment plan for a child with a DSD

referral to a court if the concerns cannot be resolved, or if there is significant on-going disagreement between parents and the treating team.

The reason for this process of clinical ethics review is to ensure that we have a robust and comprehensive decision-making process in an area of clinical practice where decisions have life-long implications for the personal identity of patients and evidence for long-term outcomes is sketchy. Treatment for DSD is a contested, emotive field that, in Australia at least, is subject to legal scrutiny. In this context, there are benefits to patients, families and clinicians in having a transparent and formal (and fully documented) decision-making process explicitly guided by ethical principles.



ETHICAL PRINCIPLE	COMMENTS RE THIS CASE
Minimise ***physical risk*** / promote physical ***well-being***	
Minimise ***psycho-social risk*** / promote psychosocial ***well-being***	
Preserve potential for ***fertility***	
Preserve or promote capacity to have satisfying ***sexual relations***	
Leave ***options open for the future***	
Consider ***views and wishes of child*** – give increasing weight as child approaches decisional capacity – if adolescent has decisional capacity (i.e., is mature minor) give same weight as would be given to wishes of adult patient	
Respect the ***parents' wishes*** and beliefs (but do not regard as fully determinative)	

Fig. 15.2 CERG discussion guide: ethical principles for use in consideration of child with a DSD

15.6 Conclusion

These principles provide a systematic approach to decision-making in a medically complex field. They are general enough to be applicable to any individual case, are not condition-specific and are not specific to current state of medical knowledge and technical capacity. The principles are flexible, and do not constitute hard and fast rules. However, they are specific enough to give some direction about priorities in decision-making. A systematic ethical approach is useful in a number of ways, both in the clinical setting and beyond. A set of agreed ethical principles embodies accepted standards of practice. It provides a framework to guide comprehensive consideration of all factors relevant to decision-making, whether this is done by individual clinicians, or by clinical ethics committees (a process that we have begun to embark on at our own centre). Ethical principles can also assist clinical practice, especially in the training of junior doctors and others involved in management, and in discussing treatment with parents. More broadly, a set of ethical principles provides clarity in an emotive, contested field. It may identify enough neutral or common ground with advocacy groups to enable more constructive dialogue, rather than conflict. It forms the basis for explaining clinical practice to people in the community, especially the affected community; and gives a tangible demonstration that

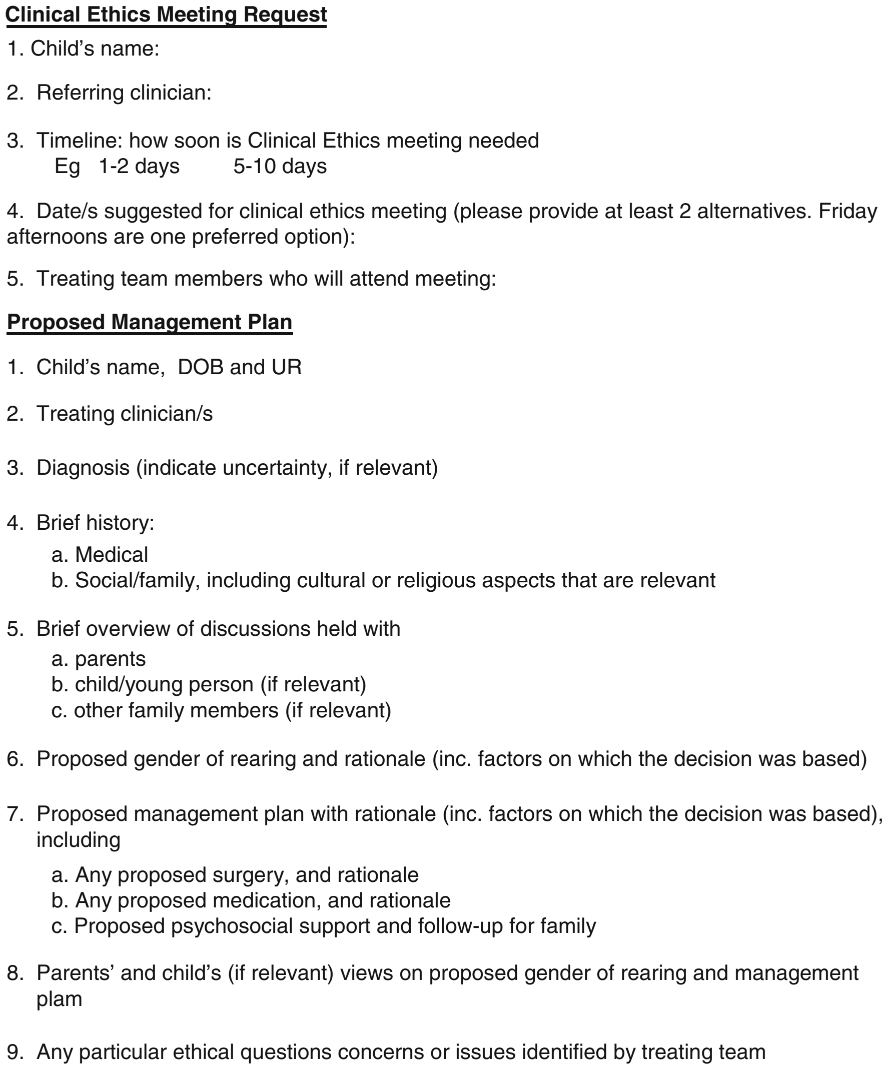


Fig. 15.3 Referral of a child with a DSD for clinical ethics review

Clinical Ethics Meeting Request

1. Child's name:
2. Referring clinician:
3. Timeline: how soon is Clinical Ethics meeting needed
   Eg 1-2 days 5-10 days
4. Date/s suggested for clinical ethics meeting (please provide at least 2 alternatives. Friday afternoons are one preferred option):
5. Treating team members who will attend meeting:

Proposed Management Plan

1. Child's name, DOB and UR
2. Treating clinician/s
3. Diagnosis (indicate uncertainty, if relevant)
4. Brief history:
   a. Medical
   b. Social/family, including cultural or religious aspects that are relevant
5. Brief overview of discussions held with
   a. parents
   b. child/young person (if relevant)
   c. other family members (if relevant)
6. Proposed gender of rearing and rationale (inc. factors on which the decision was based)
7. Proposed management plan with rationale (inc. factors on which the decision was based), including
   a. Any proposed surgery, and rationale
   b. Any proposed medication, and rationale
   c. Proposed psychosocial support and follow-up for family
8. Parents' and child's (if relevant) views on proposed gender of rearing and management plam
9. Any particular ethical questions concerns or issues identified by treating team

decisions are not taken lightly. It also provides professional guidelines to refer to in legal proceedings, government inquiries and the like, which can de-personalise issues by putting them in a broader professional context.

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The Medical Management of Disorders of Sex Development

16

Garry L. Warne and Jacqueline K. Hewitt

16.1 Introduction

The medical approach to the management of children with disorders of sex development (DSD) has undergone significant change in recent years. Successful outcomes have previously been limited by incomplete understanding of pathogenesis and natural history, and issues such as risk of germ cell malignancy and gender-identity disorder continue to be of significant importance. Past practices were also weak in relation to disclosure of diagnoses to patients and even to parents. The distress caused by this was compounded by inadequate access to psychological support.

Research has been driven by the need to improve outcomes for children with DSD, and has focused on understanding underlying genetic mechanisms. It has also yielded improved methods for diagnostic testing. The ability to identify androgen receptor gene mutations in patients with androgen insensitivity syndrome (AIS), for example, has made both carrier detection and prenatal diagnosis possible (Hughes and Deeb 2006). In addition, the diagnosis-based outcome studies that have been completed have led to an improved understanding of the patient journey. This has added greater perspective to some of the contentious debate between the medical profession and some patient advocacy groups, regarding issues such as genital surgery. Multi-disciplinary care and open disclosure of diagnosis have become the norm in many countries. The availability of psychosocial support is improving. Improved understanding of DSD is contributing to improved patient care. At the same time, it is also clear that there is still much to learn and a great deal more research is needed.

The immense impact upon both children and their families of a DSD diagnosis warrants particular attention from their physician, who carries the responsibility for practising evidence-based medicine combined with empathy, cultural sensitivity and compassion. This chapter will highlight areas in which there has been recent progress and the evidence available to inform the care of children with DSD.

The definition and diagnostic terminology used in relation to DSD were reviewed at an international consensus meeting jointly hosted in 2005 by the European Society for Paediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES). This conference, held in Chicago, brought key clinicians, scientists and patient-advocacy representatives together. The ensuing consensus statement dealt not only with terminology but also with management concepts and future research directions (Hughes et al. 2006).

Further outcome-based evidence is required in order to improve care. This research is difficult without accurate aetiological diagnoses, and it remains a fact that in a large number of children with DSD, the exact cause cannot be identified despite thorough workup (Morel et al. 2002). A focus on strategies that will enhance diagnostic accuracy should, therefore, be of importance to physicians and researchers. Until evidence from such research has been produced, the next best approach is management by multi-disciplinary teams with experience and expertise in DSD and

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who are willing to follow consensus guidelines. It is accepted that consensus guidelines are not always guaranteed to be right. They do, however, provide some security for patients and clinicians, particularly, in relation to controversial management issues such as gender assignment and surgery.

In this chapter, we describe the new classification system, outline the commonest causes of DSD, review current general concepts in management, briefly discuss gender dysphoria and primary gender-identity disorder, and offer a global perspective.

16.2 Classification System

The diagnostic terms that came out of the 2005 Chicago consensus meeting were designed to eliminate the more confusing and stigmatising elements of the previous classification lexicon. They were confusing because a number of different terms and definitions could be used to describe a particular diagnosis. A child with 46,XY DSD, for example, could be termed a male pseudo-hermaphrodite, an under-virilised male or an under-masculinised male, regardless of whether he/she had a problem with gonad development or androgen synthesis and action (Table 16.1). In addition, terms such as ‘pseudo-hermaphrodite’ and ‘intersex’ were considered pejorative.

DSDs are now defined as congenital conditions in which development of the chromosomal, gonadal or anatomic sex is atypical. This is a definition that encompasses a wide spectrum of disorders. Taken literally, it includes all types of hypospadias, ambiguous genitalia, sex reversal, Turner and Klinefelter syndromes and a range of birth anomalies such as vaginal and uterine agenesis, cloacal exstrophy and bladder exstrophy.

The disorders fall into three diagnostic groups based on peripheral blood karyotype: 46,XY DSD, 46,XX DSD and sex chromosome aneuploidy DSD. Aneuploidy DSD refers to disorders in which there is an abnormal number of sex chromosomes, such as 47,XXY Klinefelter syndrome, 45,X Turner syndrome, 45,X/46,XY mixed gonadal dysgenesis and 46,XX/46,XY chimerism. Within each of these karyotypic groups are three sub-groups of DSD defined by aetiology. These are gonadal dysgenesis, abnormal hormone synthesis or action and syndromic causes. An outline of the specific causes of DSD is represented in Table 16.2.

Table 16.1 Summary of new terminology

Title	Previous terminology
Disorders of sex development	Intersex
46,XY DSD	Male pseudo-hermaphrodite Under-virilised male Under-masculinised male
46,XX DSD	Female pseudo-hermaphrodite Virilised female Masculinised female
Ovo-testicular DSD	True hermaphrodite
46,XY complete gonadal dysgenesis	XY female XY sex reversal
46,XX testicular DSD	XX male XX sex reversal

Adapted from Hughes et al. (2007)

The new classification system has made a significant improvement, in that it creates structure and definitions that are suitable for universal use, and also eliminates odious terminology. Nevertheless, in the opinion of the authors, the diagnostic structure is still imperfect. The diagnostic stem relates to peripheral blood karyotype, but pathologists frequently group diagnoses according to gonadal development because their concern is in defining the risk of malignancy in the future. Surgeons and psychologists, on the other hand, seem to prefer classifications according to genital anatomy.

We propose the following improvement. Diagnostic documentation should be prefixed by the karyotype, followed by the gonadal morphology or diagnosis group, and then, by a rating of the genital anatomy, using a recognised pictorial scale such as the Prader scale. In addition, presence of Mullerian structures such as a vagina and uterus should be stated. For example, a neonate with ambiguous genitalia due to partial androgen insensitivity syndrome (PAIS) would be described as 46,XY PAIS, Prader 3.

16.3 Clinical Diagnosis and Approach

The most common presentation of DSD is with ambiguous genitalia in the newborn. However, DSD may also present later – in infancy, childhood, at puberty or even in adult life. The true incidence of DSD is unknown. Penile hypospadias affects 1:150 male births, Klinefelter syndrome up to 1:500 male births and Turner Syndrome in 1:2,500 female births

Table 16.2 Summary of new diagnostic structure

	46,XY DSD	46,XX DSD	Aneuploidy DSD (e.g. Klinefelter syndrome XXY, Turner syndrome X, Mosaic X/XY)
Abnormal gonad development	Partial gonadal dysgenesis Mixed gonadal dysgenesis Complete gonadal dysgenesis Ovo-testicular DSD Testicular regression syndrome Denys-Drash, Frasier and WAGR syndromes	Partial gonadal dysgenesis Complete gonadal dysgenesis Testicular DSD Ovo-testicular DSD Denys-Drash, Frasier and WAGR syndromes	Partial gonadal dysgenesis Mixed gonadal dysgenesis Complete gonadal dysgenesis Ovo-testicular DSD
Abnormal androgen action	Poor androgen synthesis or action Androgen biosynthesis defect 17β-hydroxysteroid dehydrogenase deficiency, 5α-reductase-2 deficiency, lipoid adrenal hyperplasia Androgen insensitivity Androgen insensitivity syndrome (partial, severe or complete)	Androgen excess Increased synthesis Congenital adrenal hyperplasia	
Syndromic and non-hormonal	Cloacal exstrophy, simple hypospadias	Cloacal exstrophy, vaginal agenesis	

Modified from Achermann and Hughes (2008)

Nielsen and Wohlert 1990). It is estimated that external genital abnormalities at birth requiring genetic and endocrine investigation occur with an incidence of one in 4,500 births (Hamerton et al. 1975; Sax 2002; Thyen et al. 2006). A review of a large gender referral clinic caring for children with DSD (excluding distal penile hypospadias, Klinefelter and Turner syndromes and children with multiple congenital abnormalities) found that presentation in infancy accounted for 71% of referrals (Parisi et al. 2007). Extrapolating from the above data and applying the broadest interpretation to the definition, surprisingly frequent incidence approximates 1 in 280 live births. The frequency of more severe forms of DSD, excluding less severe hypospadias, Klinefelter and Turner Syndromes could approximate 1:2,600.

The neonate with ambiguous genitalia should have specialist medical evaluation as soon as possible, as the most common cause of DSD is potentially life threatening. In addition, the birth of an infant with ambiguous genitalia is a crisis for the parents, who must deal with well-meaning enquiries from family and friends at a time when they themselves are shocked, bewildered and desperately unsure about what to say (see Chap. 19). The potential for the physician to add to their distress and cause psychological harm through ill-prepared comments and poor advice is very real.

The parents should be encouraged to delay any announcement about the child's gender until they have heard the outcome of a multi-disciplinary specialist assessment and the result of all investigations. This might take several days or even up to a week. This is because the external genital phenotype may be discordant with the underlying sex. The team of specialists would usually include a paediatric endocrinologist, urologist/surgeon and a psychologist or other mental health worker. It should be explained that informed decisions should be made about such an important issue as gender assignment and it is best to wait for specialist review and investigation results. The family should understand all clinicians involved appreciate the urgency in achieving an assigned gender.

While the parents are still being kept 'on hold' with regard to final discussion about the baby's sex, we recommend that physicians should avoid referring to the infant as 'he' or 'she' (and never use the term 'it'!) and should instead refer to the neonate as 'your baby' or the more general, 'they'. A member of the multi-disciplinary team, usually the paediatric endocrinologist, would explain the process of sex differentiation and its potential variations using simple diagrams – some excellent ones are available online at http://www.sickkids.ca/childphysiology/cpwp/genital/genitalintro.htm – preferably in the presence of a mental health professional and nurse from the ward. The family should be reassured that the child will turn out to be a boy or girl, but has taken a different path to reach his or her gender, and that the examination and investigations will help to determine the sex of the child. The family should have daily medical and psychological review and health care staff not directly involved in the care of the baby should be discouraged from curious examination.

The mother should be asked about any prenatal exposure to androgens or endocrine disrupters, if she experienced any virilisation during pregnancy, whether or not there is a family history of infant death or infertility, and about consanguinity.

Examination of the infant includes a thorough general physical examination, including ascertainment of any dysmorphic features (see Chap. 11). The stretched length of the phallus, measured from the symphysis pubis, and its circumferential girth are recorded. Mean stretched penis length – 2.5 SD in full term males is 2.6 cm for Caucasian, 2.5 cm for Indian and 2.3 cm for Chinese infants (Cheng and Chanoine 2001). The position of the urethral opening, which can be on the dorsal or ventral surface of the phallus, or in the perineum, is precisely recorded. Palpable gonads outside the inguinal canal or in the labio-scrotal folds will usually be testes, but ovaries can rarely be found in this superficial position. The anogenital distance (Holschneider and Hutson 2005), and the degree of rugosity and pigmentation of the labio-scrotal tissue are additional markers of virilisation. The degree of external genitalia virilisation can be graded using the Prader classification (see Fig. 7.1).

Appropriate first-line investigations include an urgent request for fluorescent in situ hybridisation (FISH) to detect Y chromosome material, as well as a full karyotype. This should be requested even if there is a prenatal karyotype available. A pelvic ultrasound scan should also be urgently requested for determination of internal genitalia. It should be noted that the accuracy of this investigation is highly dependent on the skill and experience of the sonographer and the availability of small probes. Measurement of serum electrolytes, 17-OH-progesterone, testosterone, follicle stimulating hormone and luteinising hormone also constitute baseline investigations. Serum Müllerian inhibiting substance/anti-Müllerian hormone (MIS/AMH), is recommended (Rey et al. 1999) but is not widely available. Further investigation is determined by the results of expert assessment and initial investigations. These may include the hCG stimulation test to assess presence of functional androgen-producing testicular tissue. The adreno-corticotrophic hormone (ACTH) stimulation test can outline a steroid hormone biosynthetic defect affecting adrenal glands as well as testicular function. Urinary steroid profiling by gas chromatography and mass spectrometry can outline the level of any enzyme defect in steroid synthesis pathways, ideally, by using a 24-h urine collection. Detailed imaging of the internal genitalia through use of magnetic resonance imaging is used in some centres, particularly in Europe. A urogenital sinugram to outline the anatomy of the lower genital tract is useful (see Chap. 14). Gonadal biopsy to exclude pre-malignant or frankly malignant changes is indicated in most infants with Y chromosome material and ambiguous genitalia. It should be noted that the absence of pre-malignant cells in the dysgenetic testis of an infant does not preclude this problem later; a second biopsy after puberty is recommended. Molecular genetic testing for specific gene mutations is being increasingly requested. Diagnostic algorithms are available to guide the use of these investigations (Brown and Warne 2005). But despite the increasing sophistication of investigation strategies, it is the widespread experience that many infants with 46,XY DSD will be left without a precise aetiological diagnosis.

It must be noted that DSD present in many guises, not only with ambiguous genitalia. They sometimes masquerade as precocious puberty, pubertal delay or primary amenorrhoea, or development of contra-sexual secondary sex characteristics, and clinical suspicion should remain present (see Chaps. 12 and 13 for details).

16.4 Commonest Causes

The three most common diagnoses where the DSD is caused by a gonadal or hormonal anomaly are congenital adrenal hyperplasia (CAH), androgen insensitivity syndrome (AIS) and mixed gonadal dysgenesis (MGD), with these diagnoses comprising 32–47% of all children with DSD caused by abnormal hormone effects (Al-Agha et al. 2001; Thyen et al. 2006; Parisi et al. 2007; Joshi et al. 2006; Bhullar et al. 2011) (Table 16.3). The small fraction of these disorders in the broader diagnostic group is due to the difficulty of accurate diagnosis in many cases. Here, we briefly outline the specific management of the three most common diagnoses.

Table 16.3 Diagnostic breakdown of reported DSD cohorts

Authors	Country	Cohort size	Study population	Common diagnoses
Parisi et al. (2007)	United States	250	Children with DSD assessed by hospital gender team (excluding Klinefelter, Turner and multiple congenital abnormality patients)	CAH 14% AIS 10% MGD 8%
Thyen et al. (2006)	Germany	80	Infants with ambiguous genitalia	CAH 18% AIS 16% MGD 9%
Al-Agha et al. (2001)	Australia	51	Infants with ambiguous genitalia	CAH 31% AIS 10% MGD 6%
Bhullar et al. (2011)	Melbourne	199	All children aged 0–10 identified with DSD using consensus statement	Perineal hypospadias 34% CAH 22% exstrophy 14%
Joshi et al. (2006)	India	109	Infants with ambiguous genitalia	CAH 28% AIS 15% 5ARD 12%

CAH congenital adrenal hyperplasia, *AIS* androgen insensitivity syndrome, *MGD* mixed gonadal dysgenesis, *5ARD* 5α-reductase deficiency

16.4.1 46,XX DSD: Congenital Adrenal Hyperplasia (CAH) Due to 21-Hydroxylase Deficiency

CAH occurs when an enzyme defect in the steroid-producing pathway of the adrenal gland leads to glucocorticoid, and sometimes also mineralocorticoid deficiency (salt-wasting CAH) (White and Speiser 2000). Steroid precursors are processed along the sex steroid pathway in the absence of the other steroid pathways, leading to over-virilisation of a female child.

Every infant with ambiguous genitalia should be assumed to have salt-wasting CAH due to 21-hydroxylase deficiency until proven otherwise. Failure to make this diagnosis in a timely manner will have a fatal outcome. A provisional diagnosis of CAH in the child with ambiguous genitalia can be made on clinical grounds: the infant, being genetically 46,XX with ovaries, will not have palpable gonads and the skin is likely to be hyper-pigmented due to the effects of excessive ACTH and related peptides. She will have a uterus. The degree of pigmentation of the skin may be hard to judge, as there is natural variation due to racial background. Examination under sunlight or white light rather than yellow incandescent light is essential. Newborn infants with salt-wasting CAH are not initially dehydrated and do not have electrolyte disturbance. Clinically significant salt depletion is seen *after* the first week of life, when most babies have left hospital and are at home. In the first week, the only metabolic disturbance that might occur is hypoglycaemia.

Newborn screening for CAH is provided in all the States of the United States and in many other countries (Torresani and Biason-Lauber 2007). It is based on measurement of 17-hydroxyprogesterone in heel-prick dried blood samples collected on day 2–3 of life. In these countries, the first contact the paediatrician has with an infant with CAH may be a referral from the screening laboratory. The presence of ambiguous genitalia does not guarantee an early diagnosis of CAH, even in countries with a highly resourced medical system. In the Texas CAH screening program, nearly 70% of cases were not clinically suspected, including 20% of females and 99% of males with CAH (Therrell et al. 1998). Newborn screening for CAH has reduced mortality, adrenal crises and incorrect sex assignment (Torresani and Biason-Lauber 2007).

A clinical suspicion of CAH, or referral from a screening laboratory, should be followed by careful clinical assessment, looking for the features that would confirm the diagnosis. Family history should seek evidence consistent with autosomal recessive inheritance. Symptoms that may be present after the first week include persistent vomiting, listlessness, poor feeding and reduced urine output, indicating dehydration. Infants with CAH are at risk of seizures due to hypoglycaemia or hyponatraemia and also of cardiac arrest due to extreme hyperkalaemia.

Confirmation of the diagnosis involves requesting an urgent serum 17-hydroxyprogesterone (17-OHP) assay, which in optimal circumstances can be completed within several hours. In most cases of classical CAH (a baby girl born with ambiguous genitalia), a greatly elevated 17-OHP result makes the diagnosis easy. If the clinical suspicion is strong and the 17-OHP result shows borderline values, an ACTH stimulation test will provide a definitive answer. In addition, we recommend collecting urine for steroid analysis to confirm that the CAH is due to 21-hydroxyase deficiency and not one of the less common varieties, such as 11β-hydroxylase deficiency. Blood for a karyotype and rapid FISH test for Y-chromosome material should be collected. Other essential tests are serum electrolytes and urea (looking for a low sodium, a high potassium and normal or only slightly high urea) and blood glucose.

The treatment of an infant with salt-wasting CAH should be provided in a centre of excellence where there is a team approach to management. We strongly recommend early transfer to such a centre, following emergency resuscitation. The paediatric endocrinologist can advise treatment with either oral or intravenous hydrocortisone, rehydration and fludrocortisone. The endocrinologist would also provide education for the parents, using resource material that is available on the internet and which can be downloaded from the following website: http://www.rch.org.au/cah_book/index.cfm?doc_id=1375. The risk of adrenal crisis during inter-current illness and how to prevent it must be clearly understood by the family. A mental health professional can assist the family through counselling to deal with the shock of having an infant of indeterminate sex and should also screen the family for social risk factors (see Chap. 19). The paediatric surgeon/urologist member of the DSD team discusses the surgical plan with the parents and other members of the team (see Chap. 17). Genetic counselling about the recurrence risk and availability of future prenatal genetic diagnosis and treatment should be made available (see Chap. 20). Prenatal dexamethasone treatment can be offered to prevent the development of genital ambiguity in an affected female foetus.

Following discharge from hospital, it is likely that the child would be followed up by the community paediatrician and the paediatric endocrinologist. Treatment is monitored using a combination of clinical measures (height, weight, appearance, secondary sexual development, clitoral size and blood pressure) and biochemical test results. We recommend a 3-monthly collection of a 9 a.m. blood sample, (delaying taking the morning dose of steroid medications until after the blood collection), for serum 17-OHP and plasma renin activity (PRA), with occasional checks using a 24-h urinary pregnanetriol.

The aims of treatment are: (1) good general health without adrenal crises; (2) normal linear growth; (3) avoidance of obesity, virilisation, Cushingoid features and hypertension and (4) normal sexual development for age. This is generally achieved by using hydrocortisone as the preferred glucocorticoid, in a dose of 12–15 mg/m^2/day in three divided doses. In all patients who had electrolyte disturbance in infancy or with persistently elevated PRA, once-daily fludrocortisone should be added. In the first 3 months of life, the normal infant diet is low in salt and all infants' kidneys are relatively insensitive to aldosterone. Levels of PRA and aldosterone in the blood are higher at this time than later in childhood. Infants with salt-wasting CAH are, therefore, relatively resistant to the effects of fludrocortisone until 3 months of age. In addition to needing doses of fludrocortisone that would usually be used in adults (0.1–0.3 mg/day), they require a dietary sodium chloride supplement (on average, 2.2 mmol/kg per day) to avoid hyponatraemia and hyperkalaemia (Mullis et al. 1990). At around 3 months, the kidneys develop greater sensitivity to the effects of mineralocorticoids and salt excretion falls. Blood pressure may rise abruptly at this time and requires close monitoring. Once the transition to greater sensitivity has occurred, the dose of fludrocortisone can be reduced to 0.05–0.1 mg/day and the salt supplement ceased.

The hydrocortisone dose should be adjusted to achieve a 3-monthly 17-OHP result <70 nmol/L. While a 17-OHP level of 70 nmol/L is far from normal, it is unlikely to be associated with hyper-androgenism, and control of androgen secretion is the true aim (Hughes 1988). Some clinics prefer to monitor serum Δ^4-androstenedione levels instead of 17-OHP. A complete suppression of 17-OHP will result in the child becoming Cushingoid. Plasma renin activity (PRA) should be maintained in the normal range and the dose of fludrocortisone is adjusted up and down to achieve this target.

The risk of adrenal crisis is greatest in children under the age of 4. Parents should be issued with a letter of introduction that can be used in the event of an emergency. It should clearly state that the child urgently requires hydrocortisone by injection (2–3 mg/kg body weight IM or IV) if she presents with vomiting, diarrhoea or dehydration; also, if she suffers significant injury, for example, a fracture, or requires surgery under general anaesthetic (Donald et al. 1993). It is common practice to provide parents with an injection of hydrocortisone to have on hand in case of emergency, so that they are never disempowered.

One quarter of girls with classical CAH have the non-salt-wasting form and have a very low risk of adrenal crisis (New 1998). Treated adequately from infancy, their development is the same as for girls with the salt-wasting form.

Long-term follow-up of girls with classical CAH treated from infancy shows that gender-role behaviour (e.g., tomboy behaviour) is usually affected by prenatal exposure to androgens. Sexual preference is sometimes affected, but gender identity is rarely affected (Meyer-Bahlburg et al. 1996). An appreciation of this is helpful in counselling teenagers with CAH. Fertility is impaired to a variable degree in women with CAH, especially the salt-losing form, although this is treatable. Referral during early adolescence to a gynaecologist experienced in CAH management is important, so that any secondary surgery to ensure an adequate vaginal opening can be planned and sexual issues are discussed in advance of the sexual debut (see Chap. 23). The endocrinologist's role is to ensure that hormonal balance is optimised. Older girls with menstrual irregularity may achieve a more regular pattern if they are treated with once-daily dexamethasone (Young and Hughes 1990). Occasionally, in an adolescent or adult patient, it may be difficult using any form of oral steroid to achieve adequate control of hyper-androgenism, without causing Cushingoid features and excessive weight gain. In this situation, there may be a place for considering bilateral laparoscopic adrenalectomy (Ogilvie et al. 2006). Hormone replacement using much lower doses is usually possible once the requirement to suppress adrenal androgens has been removed. Bilateral adrenalectomy may also improve fertility. Many women with CAH have psychosexual difficulties and rates for both avoidance of sexual activity and of homosexual activity that are higher than for the general population (May et al. 1996). (See Chap. 25).

16.4.2 46,XY DSD: Androgen Insensitivity Syndrome (AIS)

Androgen insensitivity syndrome was first described in 1953 (Morris 1953). In the *complete* form (CAIS), a person with a 46,XY karyotype and testes is born a phenotypic female. At puberty, her breasts develop and her body shape is female but she develops little or no body hair and does not menstruate, because the Mullerian structures including the uterus regressed in utero under the influence of MIS/AMH from the testes. The testes, which are usually located superficially in the inguinal area, grow during puberty and may be a source of pain or discomfort as they are easily knocked during exercise or compressed by tight clothing. They are prone to malignant change, but not before puberty; after puberty, the risk is thought to be 0.8% (Cools et al. 2006). There is debate about the timing of gonadectomy in CAIS, but there is no medical reason for this to occur before puberty and deferring it will allow natural breast development to occur. The need for it to be done at all, provided the testes are in a superficial and accessible position where they can be palpated, biopsied and studied with ultrasound, is debatable, but lifelong surveillance to detect cancer is essential (Nojima et al. 2004). As the testes are inside a patent processus vaginalis, it is important that the hernia has been repaired surgically, if a decision to leave the testes in situ is made.

A minority of women with CAIS have vaginal hypoplasia (because of Mullerian duct regression) to a degree that makes penetrative intercourse difficult (Sarpel et al. 2005). While some may require surgery to lengthen the vagina, it is not always needed because persistent and frequent attempts at intercourse can induce considerable lengthening of the vagina, simply through localised pressure (see Chap. 23).

A person with the *partial* form of AIS (PAIS) is born with varying degrees of genital ambiguity or under-development of the penis. Masculinisation at puberty is incomplete, despite considerable growth of the testes, and it is usual for breast development to occur. Parents may decide to raise an infant with ambiguous genitalia due to PAIS either as a boy or as a girl, depending on the overall appearance and size of the phallus. If raised as a girl, the testes are usually removed to avoid unwanted testosterone-mediated changes and the risk of germ cell cancer. The risk of seminoma and other germ cell cancers in PAIS testes is increased: as high as 50% when the testes are intra-abdominal and 15% when the testes are outside the external inguinal ring (Cassio et al. 1990; Cools et al. 2006). Removal of intra-abdominal testes is mandatory. If the testes are not removed (as in children raised as boys), they must be examined for tumour development on a regular basis until after the onset of puberty, then biopsied for carcinoma in situ with further action taken if pre-malignant or malignant changes are found (Muller and Skakkebaek 1984; von der Maase et al. 1987).

Gender dysphoria has been reported in as many as 25% of adults with PAIS, regardless of the initial sex of rearing (Migeon et al. 2002). Only a few, however, requested a sex reassignment.

Androgen insensitivity affects all tissues, including the hypothalamus, and therefore in individuals with AIS, the negative feedback normally exerted by testosterone on LH secretion is impaired, resulting in higher levels of circulating LH. Serum testosterone levels are considerably higher than those found in men with normal androgen receptors, and aromatisation to oestrogen is stimulated in the presence of high levels of gonadotrophins. Serum oestradiol levels, thus, exceed those found in post-pubertal males without AIS, but are lower than those found in women during the menstrual cycle. The lack of any testosterone effect on bone and relatively lower levels of oestradiol expose women with CAIS to an increased risk of osteoporosis (Sobel et al. 2006). Spermatogenesis is absent in the testes because although the local concentration of testosterone within the testis is high, as androgen action is required, the tubular response is inhibited (Yong et al. 2003; Hashmi et al. 2008).

AIS is an X-linked condition, associated with mutations in the androgen receptor gene. Phenotypic variation is related to the type of gene mutation present and the resulting alteration in the structure of the androgen receptor protein. In CAIS, the mutation results in an androgen receptor that is either absent or unable to bind any testosterone or dihydrotestosterone (DHT). Mutational analysis is usually positive in patients with CAIS, but may require sequencing of the entire gene if no gross deletion is detected. In people with a clinical diagnosis of PAIS, however, an androgen receptor gene mutation is found in only about 30% (De Bellis et al. 1994). Hundreds of different AR gene mutations have been found in AIS and structure-function relationships are complex (Gottlieb et al. 2004). In addition, over 70 androgen receptor-interacting proteins have been identified and mutations in genes regulating these have been found in a small number of AR mutation-negative patients. Females who are carriers may show mild expression in that they tend to have less pubic hair compared to other women. The incidence of CAIS is reported to be about 1:20,000 (Hashmi et al. 2008).

Explaining AIS to a young girl involves informing her that she has XY chromosomes, and for many years this was thought to be too difficult. We have developed a method based on the ideas of Goodall by which we introduce the full explanation in stages when the girl is about 12 years old (Goodall 1991). Parents can be nervous about allowing this, so we would rehearse the explanation with them at an earlier session. The issue about the XY chromosomes is dealt with by placing it in the context of other girls whose chromosomes are atypical, for example, those with Turner syndrome or triple X, mentioning also that some boys are 46,XX or 47,XXY. We do not use the traditional explanation of AIS, which emphasised negative imagery of failed male sexual differentiation. Instead, we start from the obvious, which is that she is a girl, but that she got there by a different path. We have found this to be well-accepted. Contact with other affected girls and women is extremely helpful and affirming (see Chap. 12.8).

16.4.3 Mixed Sex Chromosome (Aneuploidy) DSD: Mixed Gonadal Dysgenesis

Mixed gonadal dysgenesis (MGD) refers to asymmetrical gonad development, with a developed gonad on one side and a dysgenic or streak gonad on the other. It is commonly associated with a mosaic karyotype and sex chromosome aneuploidy. The karyotype is usually 45,X/46,XY. Children with 45,X/46,XY mosaicism show considerable phenotypic variation, from normal male, through all degrees of ambiguity to unvirilised female. Some have features of Turner syndrome and most have short stature (Telvi et al. 1999). It should be noted that most individuals with a 45,X/46,XY mosaicism do not have MGD; the male phenotype was found in 95% of antenatally diagnosed cases, 27% of whom had histological evidence of gonadal dysgenesis (Chang et al. 1990). A uterus and fallopian tubes can be present regardless of the gonadal sex and external genitalia. Gonadal dysgenesis manifests asymmetrically but both testes may have some degree of dysgenesis with raised serum FSH levels at puberty, even though during childhood one gonad appeared normal.

Children with MGD are diagnosed in various ways – by antenatal screening of pregnancies, on clinical grounds in neonates with ambiguous genitalia, at investigation of delayed puberty or short stature or when a child presents with a germ cell cancer. Examination findings may include only one palpable gonad, likely to be a testis; presence of a uterus and a testis strongly suggests MGD. The diagnosis is made with a karyotype examination, imaging and direct visualisation of the internal genitalia laparoscopically, and subsequent histological examination of the gonads (see Chap. 8).

The sex of rearing is usually concordant with the predominant external sexual phenotype, but can be difficult to assign in children who have truly ambiguous genitalia. The recommendation of the specialist team should be discussed thoroughly with the family and an informed decision made. The surgeon will then discuss the plan for genital surgery with the family.

Children with MGD are at high risk of germ cell malignancy in all gonads left in situ. The precursor of malignancy in streak gonads is gonadoblastoma, found in approximately 25% of Y-positive streak gonads (Hughes et al. 2006) whereas in testes with differentiated tubules, cancer develops from carcinoma in situ (Skakkebaek 1994). It is, therefore, recommended that gonads be removed in infancy in all children with MGD who are to be reared as girls, and any highly undifferentiated or streak gonads should be removed in those raised as boys. The consideration to leave testes in situ in a male child, when the evidence indicates a high risk of malignancy, should be made in consultation with the family. They need to be both well-informed and cognisant of the necessity for regular surveillance to prevent death from malignancy. They also need to understand that a retained dysgenic testis may also develop failure of Leydig and Sertoli cell function with time (Wikstrom and Dunkel 2008). Any retained testis should be one that is well-differentiated and should be brought into the scrotum to where it can easily be palpated every 6 months and examined by ultrasonography each year. Testicular tumours often present as painless masses found on examination. Hydroceles may be associated with a testicular tumour and should prompt further investigation (Dorfinger et al. 1997). In addition, signs of precocious puberty or gynaecomastia on regular physical examination may indicate a functional gonadal tumour. Investigation of suspected tumour involves serum tumour markers such as β-hCG, α-fetoprotein, lactate dehydrogenase, an abdomino-pelvic CT or MRI and biopsy. It is recommended that biopsy should also be performed in all in situ gonads after the onset of puberty, and if premalignant histology is found, then sperm banking be offered prior to radiotherapy (Looijenga et al. 2007). Monitoring for the development of hypogonadism should form part of the follow-up in addition to the surveillance for malignancy. Delayed or slow pubertal progression or post-pubertal lethargy and poor libido may indicate hypogonadism.

Hormone replacement therapy is required in all females with MGD, and in males who have either had bilateral gonadectomy or developed testicular failure (Warne et al. 2005). The dose and commencement of sex hormone replacement is planned to maximise height potential. If the child has been treated with growth hormone, we introduce sex hormones relatively late to maximise growth before epiphyseal closure. Females are commenced on oestrogen supplementation. A progestin is usually added after 1–2 years, or following the first break-through bleed. Testosterone replacement can be given orally, by regular intra-muscular injection or by transdermal patch. Prior to the commencement of sex steroid therapy, we recommend that all children should have a psycho-social assessment to screen for gender dysphoria (see Chap. 24). All girls should be referred to a gynaecologist at puberty (see Chap. 23).

Bone mineral density and lipid profile may be adversely affected by inadequate sex hormone replacement resulting from insufficient dosing or non-compliance, and children should be monitored for these associated pathologies. We would suggest bone mineral densitometry in patients who have experienced fractures and a lipid profile assessments at puberty and thereafter as necessary.

Psychological outcome has been evaluated recently in a small cohort of six MGD adolescents, with one female found to have gender dysphoria (Szarras-Czapnik et al. 2007). Counselling should occur regularly through childhood and adolescence, including screening for gender dysphoria.

Some females with MGD, who have good uterine anatomy and access to oocyte donation, are able to carry a pregnancy. Sperm production is highly unlikely (Robboy et al. 1982).

16.5 Summary of Management Concepts

It is widely accepted that the management of children with DSD should be performed by an experienced multi-disciplinary team. In the absence of diagnosis-specific outcome studies, difficult management issues such as gender assignment are best approached though specialist and family consensus.

As described, many children do not receive an accurate aetiological diagnosis to explain their disorder. In the absence of a definitive diagnosis, targeted care is impossible and management is best performed using the general guidelines and concepts currently accepted and described here.

Gender assignment is influenced by many factors, including diagnosis, prenatal androgen exposure, potential for spontaneous virilisation, potential for sexual function and fertility and parental attitudes and cultural background. It is, generally, accepted that most females with CAH and those with CAIS should be reared female. Children with 46,XY DSD and limited virilisation were commonly reared female in the past, however, are now mostly reared male, as evidence shows satisfaction with sexual function and gender identity in adulthood (Warne et al. 2005). Children with 5α-reductase-2 and 17-β hydroxysteroid dehydrogenase (17βHSD3) deficiencies represent a difficult group, as they are born with a female phenotype but virilise at puberty and often later identify as male (Imperato-McGinley et al. 1974; Gross et al. 1986). In the absence of strong evidence from outcome studies in other forms of DSD, gender assignment occurs after specialist recommendation and concurrence with an informed family.

Surgery for children with DSD should, wherever possible, be performed by paediatric urologists who are highly experienced in the techniques required for genital surgery (see Chaps. 17 and 18). The surgeon is responsible for explanation of the entire surgical plan until adulthood and the potential difficulties with outcome. In Y-chromosome-positive children raised female, dysplastic gonads have a high malignancy risk and should be removed in early childhood. Testes should also be removed in children with androgen biosynthetic defects who are raised as girls. The testes of girls with CAIS, however, do not need removal until after puberty because a lower risk of malignancy. In children raised male, all streak gonads should be removed without delay, and any dysgenetic testes left in situ should have regular screening for malignancy. Gonadectomy should be seriously considered in any family considered by the paediatrician to be at risk of loss to follow up. Fertility should be considered, with preservation of ovarian tissue or sperm banking if required.

Surgery on the external genitalia focuses on function as well as the cosmetic appearance. Consequently, clitoral reduction should be reserved for the more virilised children, and should aim to preserve innervation of the clitoris. Separation of the urethra and vagina (vaginoplasty) can occur at the same time. Clitoral reduction surgery remains an area of contention, as it results in loss of tissue, which could be used for phalloplasty in the case of gender dysphoria and reassignment to male sex. Vaginal reconstructive surgery should be done in infancy or delayed until adolescence, and only with informed consent. Vaginal dilatation should be avoided completely in infancy and childhood, and only considered in adolescence after discussion with the gynaecologist (see Chap. 23). In males, the complexity and difficulty of augmentation phalloplasty in adulthood should be discussed with the family at the time of gender assignment, and they should not be given unrealistic outcome expectations. Hypospadias repair can occur in early infancy or childhood using standard techniques.

Our long-term follow-up study of males who had had surgery for a DSD showed a high prevalence of persisting urological difficulties, including wetting (25%), spraying of urine (31%) and recurrent infections (25%) (See Chap. 25) (Warne et al. 2005). Women with CAH who have had genital surgery in infancy similarly have an increased incidence of urological difficulties, such as urge and stress incontinence (Davies and Creighton 2004).

Medical management involves ensuring that sex steroid replacement, if required, occurs appropriately and includes pubertal induction. In addition, those children who proceed through spontaneous puberty continue to carry a risk for premature gonadal failure. The paediatrician should also ensure follow-up of any disorders associated with inadequate sex hormone replacement such as low bone mineral density and dyslipidaemia, and any associated syndromic features such as cardiac anomalies, vision or hearing defects. A group of syndromes caused by mutations of a similar gene region share problems with renal and gonad development and some carry high risk for Wilms' tumours of the kidney as well as germ cell malignancy of the gonads. These disorders include Denys-Drash Syndrome, Frasier Syndrome and WAGR Syndrome (Jadresic et al. 1990) (see Chap. 10).

Finally, psychological support must be provided to the family at initial diagnosis, and regularly for the affected child throughout their life. Disclosure should occur in stages appropriate to the developmental level of the child and begin from the age of 3 or 4. If the parents find disclosure difficult, they should be supported by their physicians and psycho-social allied health staff to achieve an open disclosure of the child's disorder to the child. Psychological support is particularly important at puberty and should include assessment for gender dysphoria. Psychological support of children with DSD and their families is arguably the most important aspect of care and was highlighted as the most deficient in a patient follow-up survey (unpublished data). It is hoped that with improved psychosocial care of children and adolescents with DSD, we will see a significant improvement in outcomes.

16.6 Gender Dysphoria in Relation to DSD

As shown in a number of long-term outcome studies, some adults who had been surgically treated for a DSD as children develop gender dysphoria, that is, they feel a persistent and unpleasant insecurity about their gender identity (Cohen-Kettenis 2005a). For some, the discomfort is so extreme that they actively seek change of gender and a sex-change operation. The incidence of gender dysphoria varies depending on the type of DSD and the effectiveness of hormonal treatment in early life, but there are other factors yet to be clarified. Most papers published to date have focussed on the small number of patients seeking a sex change and comparison between different DSD on the number who are simply unhappy about their own gender to a lesser degree, is currently not possible.

Very few girls and women with classical CAH, treated with effective suppression of androgens from infancy, identify as male, but the number wishing to change gender from female to male rises if hyperandrogenism is allowed to exist for long periods during childhood and it is common to encounter this in developing countries. (Warne and Raza 2008).

Gender dysphoria has also been reported following treatment for mixed gonadal dysgenesis and it has been said that those raised male experience less psychopathology than those raised female (Szarras-Czapnik et al. 2007). This is perhaps because the surgery to fashion male genitalia conserves all external tissues and thus preserves options for surgical review in the future, whereas feminising genitoplasty involves the removal of some genital skin and erectile tissues, making a later reversal extremely difficult.

As is well-known, spontaneous change of gender identity from female to male occurs after the onset of puberty in 46,XY children with 5α-reductase-2 deficiency and similarly in children with 17β-hydroxysteroid dehydrogenase (17βHSD3) deficiency (Cohen-Kettenis 2005b; Rosler 2006).

Among patients with genetically confirmed PAIS treated at the Johns Hopkins Hospital in Baltimore, adult gender identity conformed in the majority to the initial assigned gender, but nearly 25% of adults surveyed expressed some degree of dissatisfaction with their gender, regardless of whether they had been raised as boys or girls (Migeon et al. 2002). It is tempting to speculate that parental styles of rearing might have contributed, but evidence for this is lacking. How the milder forms of gender dysphoria would respond to counselling or psychotherapy is also not known. Women with the complete form of AIS, on the other hand, do not suffer from gender-identity disorder, despite having inguinal testes, an XY karyotype, testosterone levels that are significantly higher than those of males, and in many cases, a feeling of not being complete as a woman because they have no uterus. The extent of gender dysphoria in patients with DSD, therefore, relates at least in part, to androgen action in the brain.

16.7 Primary Gender-Identity Disorder

Some children express the gender identity of the opposite sex from the earliest age, despite having normal anatomy, hormone levels and sex chromosomes. Twin studies suggest a small but significant genetic contribution to the aetiology of the condition (Segal 2006), and MRI studies of the brain have identified some fairly subtle differences between trans-sexuals and non-trans-sexuals in the size of certain nuclei, such as the bed nucleus of the stria terminalis (Zhou et al. 1995). Persistent and profound gender-identity disorder (trans-sexual type) is included in the DSM-IV classification of mental disorders. It is regarded by most workers in the field as a developmental human variation in which, for reasons not understood, the gender identity of the affected person is fixed as the opposite of their anatomical sex. No form of therapy is able to change the gender identity. Patients have a strong and persistent desire to change their social gender, to live as the other sex, and in almost all cases, to have surgery and hormonal treatment to bring about the desired bodily changes. Medical and paramedical services are required to:

- Establish the diagnosis
- Assess the patient's cognitive abilities and the social circumstances
- Develop a holistic management plan including all aspects of medical care, psychological support for the child and family
- Provide social support and liaison to allow the integration of the child into school and community, while shielding him/her as much as possible against discrimination and abuse

Later, the plan would include assisting the young person to decide about any physical transition that might be considered and providing access to legal advice as needed.

16.8 World View

The management of DSD varies from country to country (Warne and Raza 2008). Medical facilities in most low income countries are basic but expensive, levels of education are low and health professionals are unable to access literature that would help them keep up-to-date. Health budgets are spent on public health priorities such as immunisation and clean water, or misused on expensive high-tech equipment that benefits very few. Poor families only use medical facilities as a last resort, after all forms of alternative treatment have been exhausted. Traditional values and beliefs prevail and there may be deeply held prejudice against individuals whose sexual development is atypical. In some cultures, an infant born with any congenital anomaly has a greater chance of dying due to neglect and a child known to be infertile would be seen as having little value. Essential medicines such as hydrocortisone and fludrocortisone were only very recently added to the World Health Organization's 'List of Essential Medicines for Children' and are, therefore, not yet available in developing countries that rely on this list as a guide for importation and licencing. Lack of these medicines makes it impossible for more than a few children with salt-wasting CAH to survive.

In very low-income countries, girls who survive with non-salt wasting CAH may not see a doctor for the first time until they are in mid- to late childhood, by which time they are tall and muscular, have an advanced bone age, are severely virilised with a grossly enlarged clitoris, and in many cases a deep voice. Their high androgen levels affect the cerebral cortex, with effects on gender-role behaviour and ultimately gender identity. Maturation of the hypothalamus is also affected. High circulating levels of progesterone suppress gonadotrophin secretion. The commencement of glucocorticoid replacement therapy causes the progesterone levels to fall, releasing the hypothalamic-pituitary axis from suppression, and gonadotrophin secretion rises. The girl then experiences central precocious puberty, with further advancement of bone age and loss of adult height potential. Ideally, this would be treated with a GnRH analogue, but this expensive treatment is unfortunately out of the reach of most families in poor countries.

The overall view of DSD in low-income countries is one of extreme misery. A great deal could and should be done to alleviate this suffering, through research, strategic development aid, advocacy, community education and specialised training programmes for medical and allied health professionals.

16.9 Conclusion

The management of a patient with a DSD is complex and requires skills beyond the capacity of any individual clinician. A co-ordinated multi-disciplinary approach with a strong contribution from mental health professionals is needed if a good outcome is to be obtained. The establishment of large international patient databases such as EuroDSD, which is based in Germany, is laudable as they allow better tracking of individual patients over time, facilitate collaborative research and concentrate expertise where it is needed.

The ethics of medical practices in relation to surgery, disclosure policies and sex assignment have been under challenge from some advocacy groups for more than a decade. In Australia, this has led to Justice Department involvement. A proposed policy under discussion is that clinicians should refer every infant with DSD to the courts for judgement on surgical management. The authors do not feel that this is an appropriate way to approach the issues and controversies, and have developed an internal but independent ethics committee within our institution to review all the cases before irreversible treatment (see Chap. 15).

It is the obligation of all clinicians caring for patients with DSD to ensure that everything they do is evidence-based and patient-centred. There are real issues, and involvement of the wider community in the debate is an advance. More rational dialogue between multidisciplinary care providers, bioethicists and greater representation of patients and their families will only lead to improvements in care. We await further developments with interest.

16.10 Future Perspective

In the next 5–10 years, it seems highly likely that emerging technologies such as micro-array will have led to the discovery of more of the genes involved in testicular differentiation and ovarian differentiation. We may also understand the biological basis for gender identity and its disorders. If this prediction eventuates, it will be possible to quickly screen all of the 20,000–25,000 genes in the DNA of any infant found to have a DSD. An accurate diagnosis, and even a prediction of long-term outcome, will be possible in the majority. Every developed country will have established multi-disciplinary services offering seamless care for people with DSD from birth to old age. People with a DSD will feel less stigmatised because the community will be better educated on the subject. Inexpensive technologies for hormone measurement suitable for developing countries will have been developed; education and training of health professionals in some of the poorest countries will have improved outcomes for patients although they will still be disadvantaged. Clinicians should continue to be aware of the effect of DSD on children around the globe.

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Surgical Treatment in Infancy

17

John M. Hutson

17.1 Introduction

The surgical management of DSDs is complex, and is best managed with a team approach, so that the number of surgeons involved is relatively small, enabling them to maintain expertise. Diseases that are common can be managed by many different doctors, even if they are complex, as their frequency allows different practitioners to become competent by practice. By contrast, disorders, which are both rare and complicated, are difficult to manage by the occasional operator, as they are not exposed to the clinical variations frequently enough to become expert in their management. One solution to this problem, which is occurring worldwide, is in the development of specialised centres where rare, complicated disorders can be managed by a special team.

In our own hospital, DSDs have been surgically managed by only 4–5 surgeons over 30 years (Hrabovszky and Hutson 2002). This concentration of expertise has allowed us to maintain a very high standard of surgery, which is demonstrated in our outcomes as measured in both short- and long-term follow-up studies (see Chap. 25). This super-specialisation occurred in our own institute much sooner than in many other places in the world, and this is likely to be one of the key factors in our better outcomes.

The recent discussion in both the media and medical circles to limit surgery in this area is likely to be a direct consequence of the fact that in the previous generation most children in other centres had surgery done by people with no special expertise in the area. It is easy to forget that CAH was only discovered in 1953, and that reasonable surgical treatments of this disorder were not available until the 1960s or 1970s. Not surprisingly, the first few cohorts of patients from the 1960s and the 1970s have had a mixed outcome, with many patients now as adults unhappy with the standard of their previous management in childhood (Farkas and Chertin 2001). In some parts of the world, response to this public pressure has been to suggest that treatment should be delayed until adolescence, and this is particularly true in the United Kingdom and parts of Europe as well as the United States of America. In Australia, our response to this public pressure has been to recommend increasing referral of patients to specialised centres, so that the children can be given treatment at world standard. A more detailed discussion of the pros and cons of treatment in infancy is given in Chap. 21. However, the reader should be aware that we have continued in our own department to advocate for early surgery because our short-term and longer-term results support this practice, as described in Chap. 25 (Warne et al. 2005; Crawford et al. 2009; Lean et al. 2005).

Our first long-term review of our patients was done in the 1980s, and this demonstrated many things that should be avoided in childhood (Luthra and Hutson, unpublished). When our first cohort of adult patients was interviewed we found that many patients vividly remembered having frequent genital examinations in later childhood, which they found very disturbing. In addition, they found post-operative vaginal dilatations very upsetting. We, subsequently, realised that these are actually completely unnecessary when surgery is done in infancy, and are best left to adolescence when the

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patient herself can supervise this if required. In addition, we found that the patients appreciated regular follow-up by the surgeon involved in the reconstruction, as it enables them to discuss the anatomical details directly with the doctor who is most familiar with their anatomy. If the patient is being raised as a girl our adolescent gynaecologist is involved at a very early stage, and will commonly assist at the surgery in infancy (see Chap. 23). This enables transfer to gynaecological care in early adolescence much simpler, as the family have already met the gynaecologist and discussed the gynaecological issues earlier in childhood. The other major benefit of our first major review in the 1980s was the realisation that we needed an open disclosure policy with both the parents and the patients themselves. It became very clear that patients needed a low-key, matter-of-fact honest approach rather than being treated as ‘freaks’ in front of assembled medical students. This aspect of our psychological management is discussed at length in Chaps. 16, 22 and 24.

17.2 Feminising Genitoplasty

The surgical repair of infants being raised as females includes the following principles:

1. Reduction of the erectile tissue of the enlarged phallus with preservation of the glans and its neuro-vascular supply.
2. Creation of a normal looking introitus with labia minora and labia majora.
3. Vaginoplasty to provide an adequate opening in the introitus for the vagina.

17.2.1 Clitoroplasty

The principal surgical procedure to manage enlargement of the clitoris until the 1960s was excision of the clitoris or clitoridectomy. Unfortunately, amputation of the clitoris left a normal female-appearing introitus, but removed a crucial organ for adult sexual function. This led to several new operations in the 1960s and 1970s to bury the clitoris in the mons. These procedures preserved neurovascular supply and function, and produced a good cosmetic effect in early childhood, but led to painful erection during sexual arousal in adult life. Such techniques have now been mostly abandoned for this reason. The next phase of development was reduction clitoroplasty, where part of the erectile tissue was removed with preservation of the glans. A number of different variations were described, which aimed to preserve the dorsal neurovascular bundle but reduce the volume of the erectile tissue in the shaft of the clitoris (Schnitzer and Donahoe 2001).

In the early 1970s Robert Fowler, who was the first surgeon in our department to have a special interest and expertise in the management of children with DSD, devised a novel operation for reduction clitoroplasty. This was a huge advance in comparison with other operations at the time, and has given such good results that it is still in use with minor modification nearly 40 years later (Hutson et al. 1991). The principle of this technique is to reduce the girth of the clitoris by excision of some of the erectile tissue on the ventral surface after placing tourniquets around each corpus cavernosum. As the neurovascular bundles are on the dorsal surface of the shaft, the ventral surface can be trimmed without risk to blood supply or sensation. If the glans of the clitoris is enlarged this is also excised in the coronal plane, and the glans is then reconstituted into a cone. The clitoris is folded upon itself to create a hairpin bend so that the raw surfaces on the ventral surface of the corpora cavernosa are approximated by watertight suturing down each side. The position of the fold is arranged so that the glans is placed just superficial to the bifurcation of the crura. This technique creates a clitoris that is in the right position and of the right size, and has no tendency to protrude like a male erection during sexual arousal. In addition, because the dorsal surface of the clitoris has been left untouched there is no interference with the neurovascular bundle, thereby avoiding ischaemic injury to the glans and also any risk of de-nervation of the glans.

Creation of labia minora occurs by using the skin of the shaft of the clitoris, which is divided in the midline and brought down on each side of the glans and newly-formed introitus (Roberts and Hutson 1997). The inner layer of the foreskin is not excised so that it can be reused to constitute a hood over the glans. The detailed operative steps are described separately with the figures (Fig. 17.1a–p).

17.2.2 Vaginoplasty

Creation of an adequate vagina is thought by most surgeons to be dependent upon the level of entry of the existing vagina into the common urogenital sinus. Many

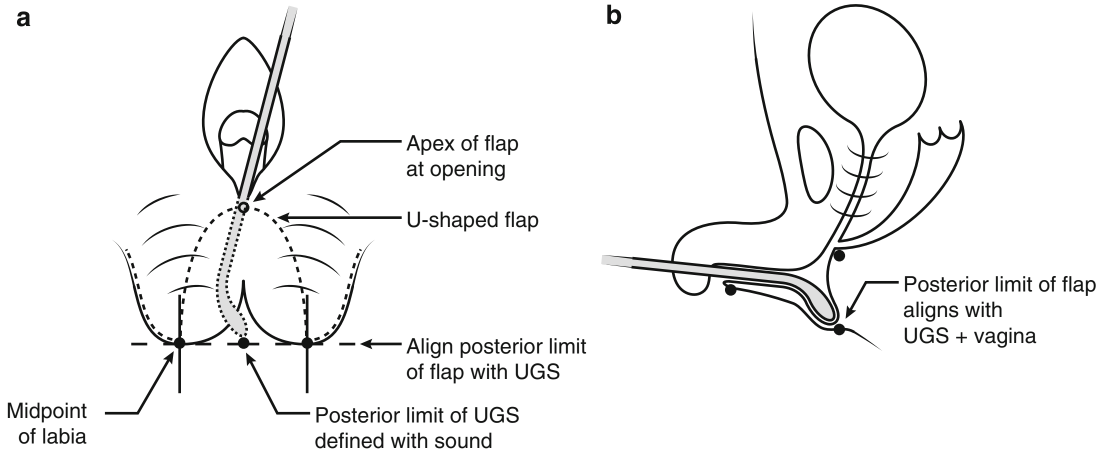

a
Apex of flap at opening
U-shaped flap
Align posterior limit of flap with UGS
Midpoint of labia
Posterior limit of UGS defined with sound
b
Posterior limit of flap aligns with UGS + vagina

Fig. 17.1 Standard feminising genitoplasty as performed at the Royal Children's Hospital. (**a**) The key to identifying the skin landmarks for creating the incisions for a vaginoplasty. A urethral sound is passed into the urogenital sinus to identify the posterior limit of the urogenital sinus (UGS), which is running subcutaneously similar to the anterior urethra in a male. (**b**) The posterior limit of the sound is in alignment with the opening of the vagina in the urethra. (**c**) The skin is marked in the midline at the posterior limit as well as at the same level in the midpoints of the labio-scrotal folds. The U-flap is marked as shown, with lateral extensions outlining the rounded edge of the labia in the skin crease marking the attachment of Scarpa's fascia. (**d**) Although the length of the UGS may be long, and increases in proportion to Prader score (*A*), the distance from the surface to the vaginal opening (*B*), remains relatively constant. (**e**) The UGS is divided in the midline to its posterior limit once the U-shaped skin flap has been raised. This exposes the hymen at the back of the urethra, allowing a small Foley catheter to be inserted into the vagina to provide traction. The midline incision in the UGS can now be continued through the hymen and up the posterior wall of the vagina until one reaches the dilated proximal vagina (the masculinised lower vagina is always too narrow). (**f**) The U-flap is sutured to the apex of the incision in the posterior vaginal wall, completing the vaginoplasty. The incisions for the clitoroplasty are shown. Importantly, the inner foreskin is left with the glans, so that the clitoral hood can be reconstructed later. The glans is otherwise circumscribed along the coronal groove, ventrally, and the incisions are extended to meet with the anterior ends of the UGS incisions, thus permitting complete mobilisation of the glans. (**g**) The shaft skin is divided in the midline up to nearly the base of the shaft, and held with stays. The shaft is mobilised until the suspensory ligament (*Z*) is identified and divided. Anteriorly, the mucosal strip of the UGS, along with its attached corpus spongiosum (*X*), is mobilised off the front of the corpora cavernosa. There is a plane here, which is almost completely avascular. The corpus spongiosum is lifted off until the bifurcation of the crura is reached (*Y*). (**h**) The subcutaneous tissue in front of the symphysis pubis is divided to expose the symphysis itself (*W*). (**i**) A right-angle forceps is inserted under the corpora in the midline superiorly, and using palpation for guidance the tip of the forceps is brought through anteriorly, allowing vascular loops to be placed around each corpus cavernosum. This provides vascular control of the entire shaft. (**j**) The anterior surface of the glans and shaft is excised under tourniquet control. The amount of glans and erectile tissue removed varies, depending on the original severity of virilisation. (**k**) The glans is reconstituted with 6/0 interrupted sutures, leaving the raw surfaces of the corpora still exposed. (**l**) The clitoris is folded over so that the raw surfaces are approximating each other, and then sutured together down each side with a continuous water tight suture of 6/0 or 5/0. This will join the fascia at the base of the shaft (just above the bifurcation with the coronal groove area of the shaft). (**m**) The clitoris is now reconstructed with a conical glans of appropriate size and shape, and a hairpin shaft. The vascular loops should be released at this time to ensure haemostasis. (**n**) The hairpin fold, is now attached to the periosteum of the symphysis pubis with two sutures, being careful not to anchor it so tightly that the dorsal clitoral arteries are occluded at the hairpin fold. (**o**) The shaft skin is reattached to the shaft, with a deep suture (B -> B2) and a superficial suture (A^1 -> A^2), joining the pubic skin at the apex of the foreskin flaps to the inner layer of the foreskin over the glans. The UGS mucosa and corpus spongiosum is reattached under the tip of the glans. Finally, the shaft and foreskin flaps are brought down on each side of the now open UGS, joining C^1 to C^2. (**p**) Once the medial side of each flap has been attached to the glans, UGS mucosa and side of the vaginoplasty U-flap, the lateral side requires suture, between the shaft flaps (future labia minora) and the labia majora. Starting anteriorly, the suture picks up each skin edge as well as the deep soft tissues, to pull in the suture line to create a fold between labia minora and majora. Finally, the posterior edge of the labia majora needs trimming, as appropriate. Excision of the redundant posterior labial skin, which is often wrinkled and pigmented, and suture of the edges are in two layers to create rounded labia posteriorly, along the line of attachment of Scarpa's fascia. A deep layer of sutures ensures that there is not major wound breakdown when the superficial skin stitches are resorbed

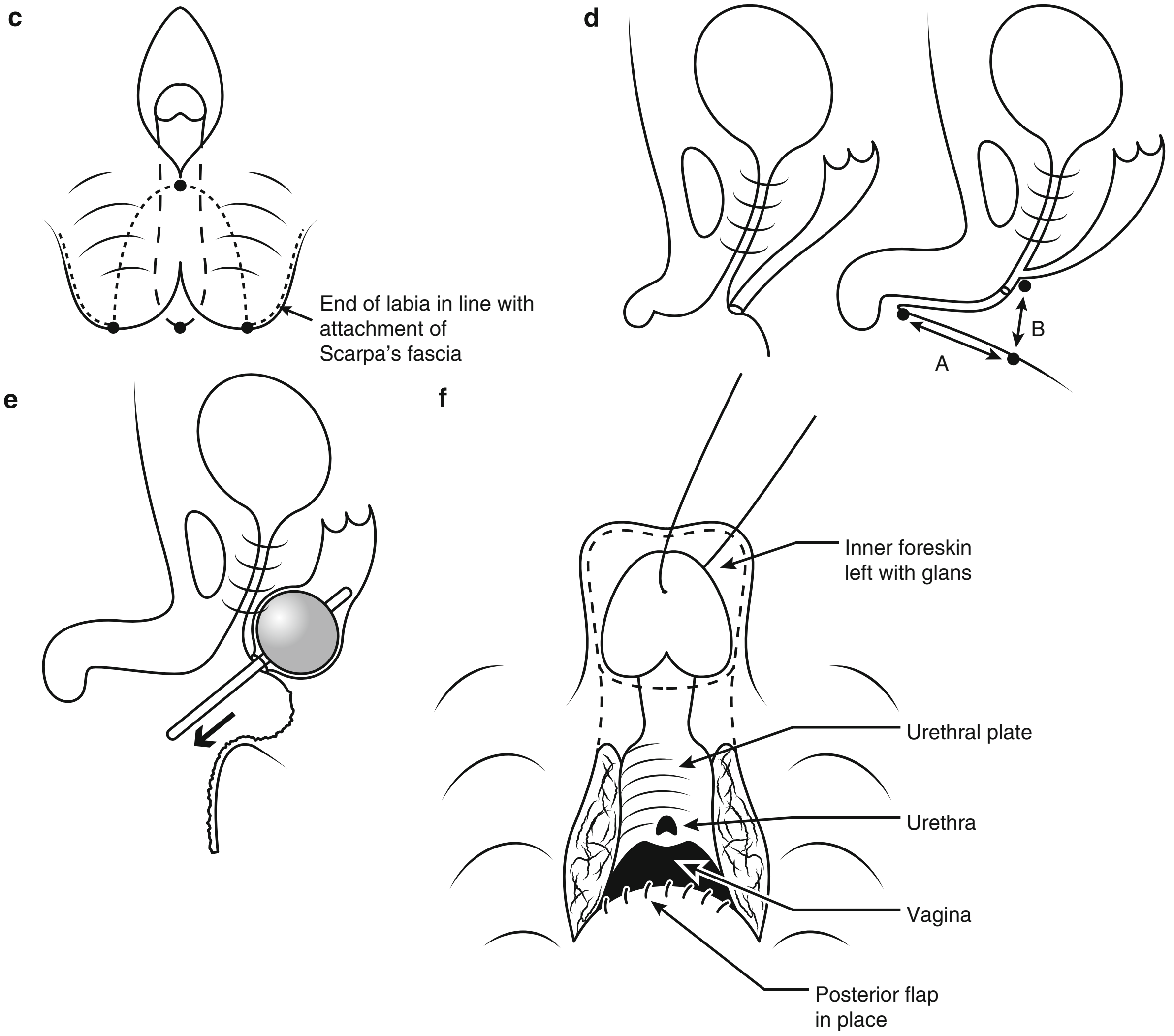
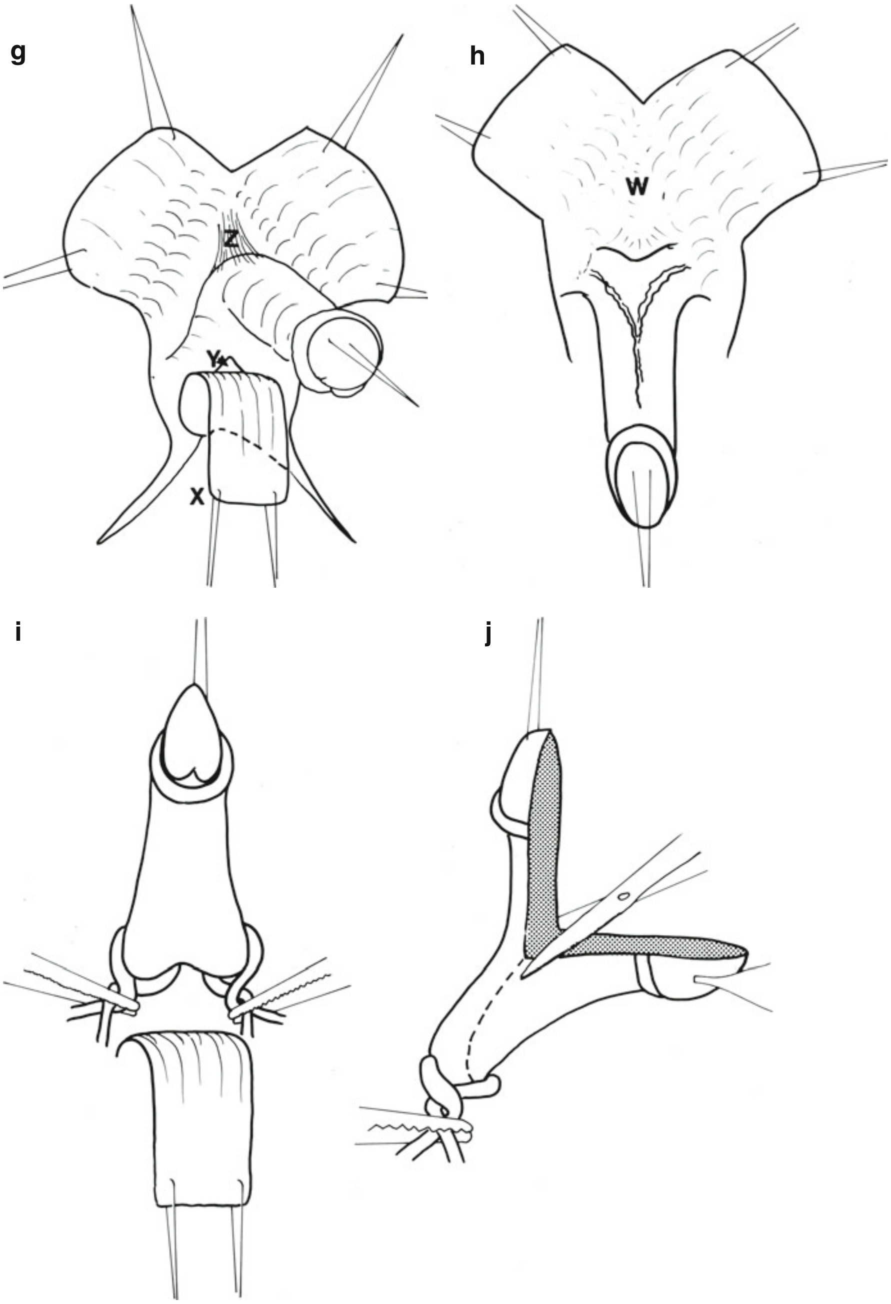

c
End of labia in line with attachment of Scarpa's fascia
d
B
A
e
f
Inner foreskin left with glans
Urethral plate
Urethra
Vagina
Posterior flap in place

Fig. 17.1 (continued)

urologists recommend endoscopic examination and a retrograde urethrogram to identify the connection between the genital and urinary tracts. This is thought to be necessary to be certain whether or not the vagina enters the urogenital sinus distal or proximal to the external urethral sphincter. If the vagina was found to enter the urogenital sinus above the sphincter then a more complex operation than a simple V-Y vaginoplasty was thought to be necessary (Hendren 1998). Certainly, the distance of the vaginal opening from the surface is much greater in babies with more severe virilisation, although in babies with CAH it is extremely rare for the vagina to enter the urethra above the sphincter, even when the Prader score is 4 or 5. This can be seen on the urogenital sinugram, where the connection is a long way from the opening of the urethra, and is nearly always at or just above the junction between the anterior urethra and the posterior urethra. This has led us, therefore, to use flap vaginoplasty in all but the most severe anomalies, as the distance from the end of the vagina to the skin is very little different between minor and more severe masculinisation. Some

Fig. 17.1 (continued)



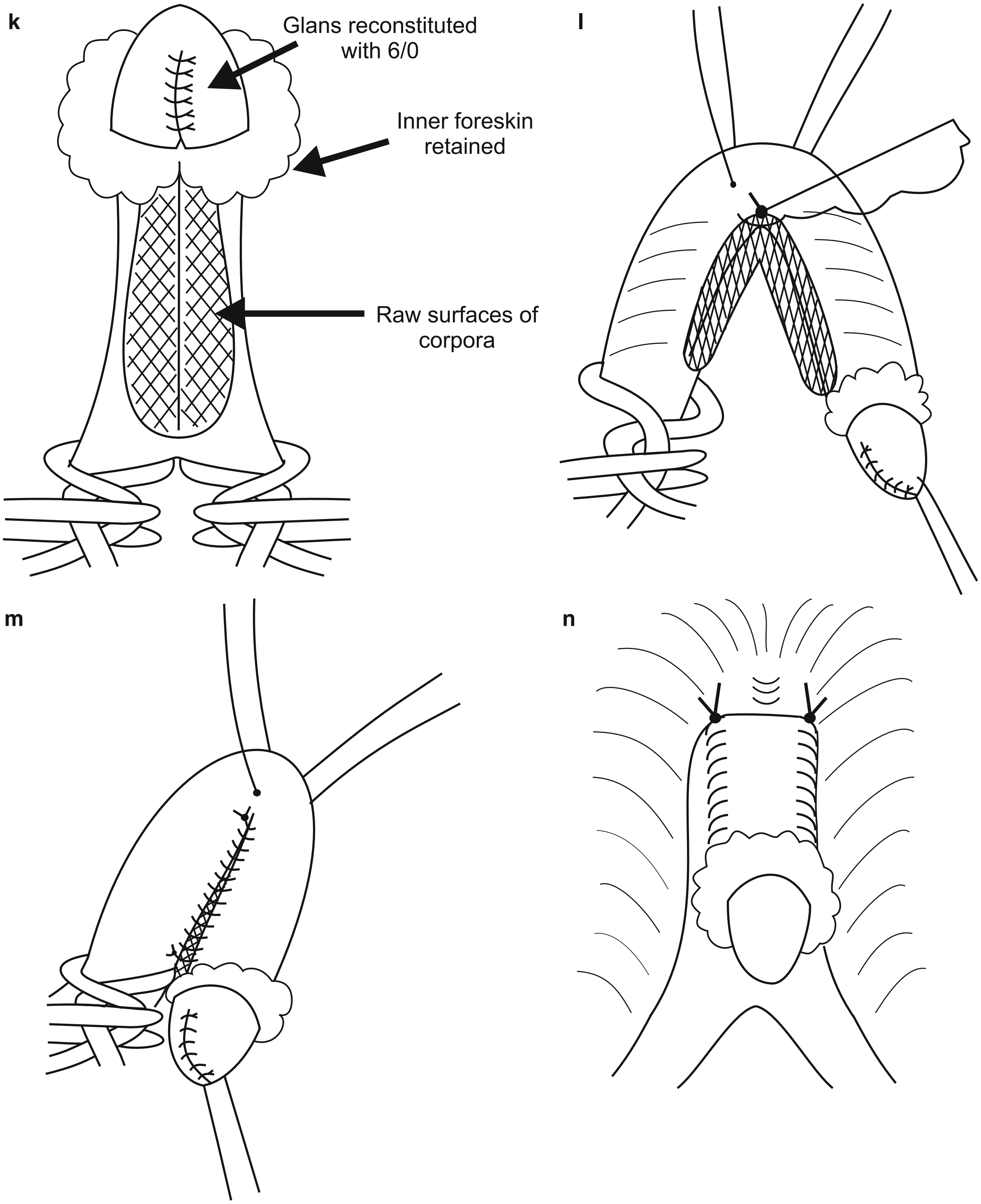
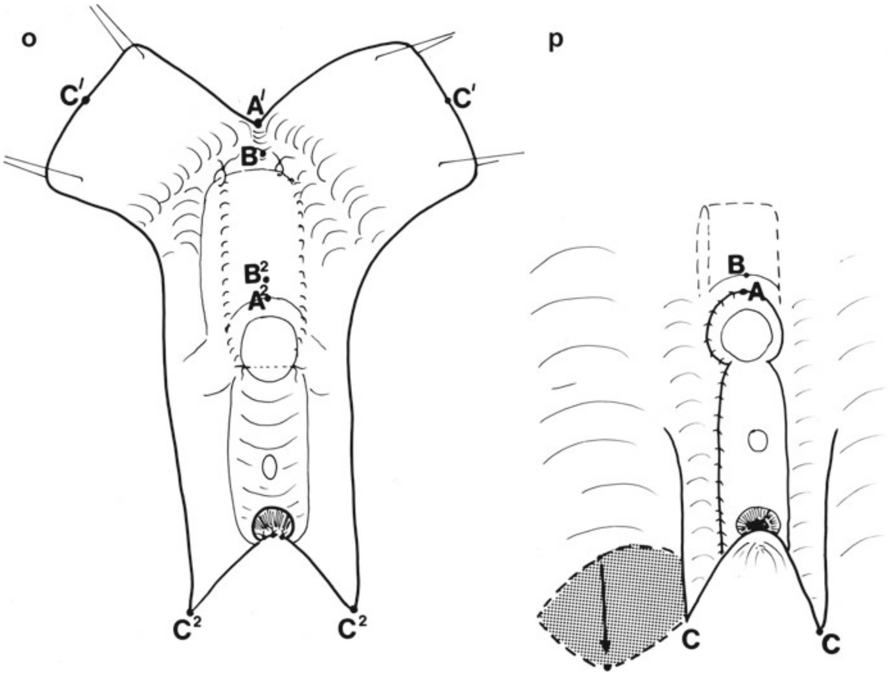


Fig. 17.1 (continued)

Fig. 17.1 (continued)



surgeons recommend commencement of vaginal dilatations a few weeks after surgery, but, as previously mentioned, we have deliberately avoided this, in the belief that regular dilatations are not only unnecessary in infancy but also may even contribute to increasing scar tissue, which might be a disadvantage in adolescence. In addition, the process is very stressful for parents and any child old enough to understand what is happening. Although a perineal pull-through operation has been described for situations where the vagina is entering very high in the posterior urethra (Hendren and Atala 1994; Tillem et al. 1998), in our experience, this is extremely rare and such operations are mostly unnecessary. In Chap. 25, we describe our medium- and long-term results using the standard method originally developed by Robert Fowler, with our immediate results shown in Fig. 17.2.

Passerini-Glazel (1989) has described an operation for reconstruction of the vagina using the skin of the urogenital sinus inverted back inside and anastomosed to the opening of the vagina, which is occasionally useful. Pena has also described surgical reconstruction of the high vagina using a posterior sagittal approach dividing the anorectum after a temporary colostomy (Pena and Hong 2003). This approach has enthusiastic advocates as well as critics. In some very complicated cases, the vagina is

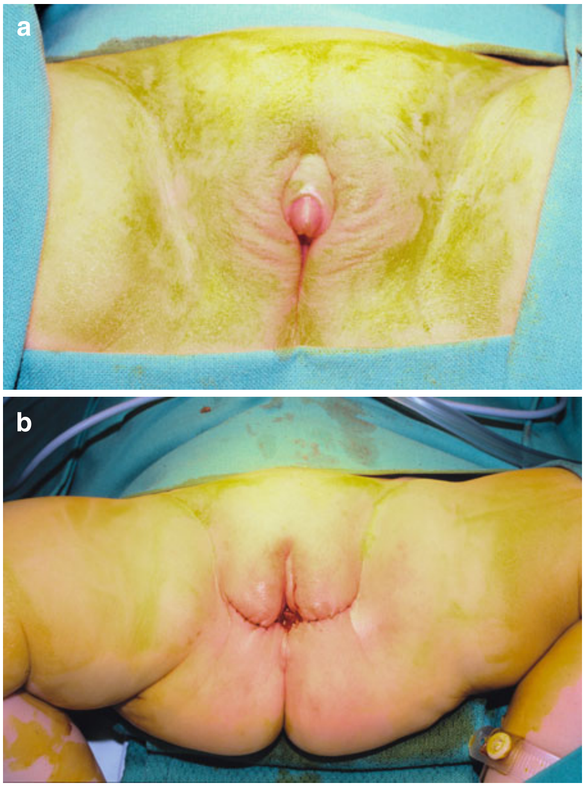


Fig. 17.2 Pre-operative (**a**) and immediate post-operative (**b**) appearance in a patient with Prader2 virilisation

so rudimentary that surgical reconstruction, particularly in infancy, should be deferred until a definitive operation can be done once in adolescence. These procedures are discussed in Chap. 23.

17.3 Masculinising Genitoplasty

Reconstruction of the genitalia for male gender of rearing depends on the following principles:

1. Hypospadias repair
2. Orchidopexy
3. Correction of the bifid scrotum and of the pre-penile position of the scrotum
4. Excision or separation of retained Müllerian duct structures from the urethra
5. Excision of any discordant gonadal tissue

The principles of hypospadias repair are the same as that elsewhere in urology, with correction of chordee, re-arrangement of the skin using Byars flaps, as described by Durham Smith (1981, 1983) or grafting of a future urethral tube, as described by Bracka (2011 and Manzoni et al. 2004). The various techniques do not need to be discussed at length here, as there is nothing significantly different from standard practice as described in urology texts. In patients with a pre-penile, bifid scrotum transposition of the scrotal skin to the perineum may be performed as part of a hypospadias repair, or at a separate operation. As most patients with this degree of abnormality require a two-stage operation, scrotal transposition would usually be done at the same time as creation of the urethra. Another important principle of hypospadias repair in these children is to ensure that the vaginal remnant, if present, has been removed or disconnected from the posterior urethra, before creation of the urethral tube. If the vagina is left in situ, the creation of the urethra will cause significant back-pressure on passage of the urine that the vagina will fill with urine on micturition. This is likely to lead to recurrent urinary tract infections and may predispose to break down of the hypospadias repair.

Recently, management of the retained vaginal remnant has been done laparoscopically, with either excision at the posterior wall of the urethra, or ligation and division of the vagina, but with the structures left in situ. This has been done to maintain all options for the future, in case the patient wishes female gender later in childhood or adolescence. This strategy is too new to have any long-term follow-up results on efficacy, but will require confirmation that retention of female internal genital ducts does not predispose the boy to increased risk of female genital tract pathology.

Where resection is selected as the treatment option, the genital remnant can often be excised via the perineum, as the confluence with the distal common urogenital sinus is frequently quite close to the perineal skin. Complete excision is possible up to the connection with the vas deferens, which usually drains into the cranial end of the cavity. Alternatively, sub-mucosal resection, leaving the muscular wall in situ, can also be done easily, which decreases the risk of anterior rectal wall injury. The latter can be prevented by periodic insertion of a finger into the rectum to palpate the anterior wall to estimate the proximity of the dissection plane to it.

17.4 Conclusion

The surgical reconstruction of ambiguous genitalia is both complex and controversial, and should only be undertaken with full parental consent and adequate discussion of the alternatives. In addition, because of the severe psychosocial and emotional consequences of a poor outcome, it needs to be restricted to specialised centres with the requisite expertise.

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Laparoscopy for DSD

18

John M. Hutson and Chris Kimber

18.1 Introduction

Laparoscopy has limited use in patients with DSD, many of whom are diagnosed without direct visualisation of the internal genitals. Congenital adrenal hyperplasia (CAH), for example, rarely needs laparoscopy as the internal genitalia are normal (as confirmed on ultrasonography) and reconstruction of the external genitals is done via the perineum. There are, however, a number of clear situations where laparoscopy is indicated.

18.2 Indications for Laparoscopy

The following are the three main reasons for laparoscopy in patients with DSD:

1. Diagnosis of intra-abdominal anatomy when this is in doubt.
2. Biopsy or excision of dysplasic gonads containing Y chromosomes
3. Excision (or disconnection) of internal genital ducts as a single procedure or as part of an abdomino-perineal reconstruction.

18.3 Diagnosis of Internal Genital Anatomy

This is required in patients in whom chromosomal analysis shows the presence of a Y chromosome, as seen in a range of (mostly rare) conditions (Table 18.1). This is because normal or dysplasic gonads containing the Y chromosome have: (1) a variable degree of testicular differentiation and (2) a propensity to undergo progressive dysplasia, possibly related to the intra-abdominal temperature (37°C).

18.3.1 Androgen Insensitivity Syndrome (AIS)

Androgen insensitivity is caused by an X-linked mutation in the androgen receptor, making the target tissues more or less insensitive to circulating androgens. It is the most common cause of under-virilisation in which patients with 46,XY chromosomes and otherwise normal testes do not have a normal male phenotype. In the complete form of insensitivity (CAIS) the androgen receptor is completely non-functional, and the affected infant is a girl with external genitals that are unambiguously female, and the vagina is slightly shorter and blind-ending. Both Müllerian and Wolffian ducts are absent, so there is no uterus or vaginal vault. Secondary sex characteristics are normal female apart from absence or severe deficiency of pubic and axillary hair, as testosterone is converted in peripheral tissues into 17β-oestradiol.

Patients with CAIS may present early in infancy or childhood as a female with an inguinal hernia (often containing a gonad) (see Chap. 12), or more commonly, as adolescents with primary amenorrhoea (see Chap. 13).

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Table 18.1 Y chromosome-containing conditions where laparoscopy is useful

Condition	Karyotype	Pelvic anatomy
CAIS/PAIS	46,XY	Testes in pelvis/inguinal hernia, absent vas deferens and uterus
MGD	45,X/46,XY	One testis (dysplastic) and vas, one streak and uterine tube
Ullrich-Turner	45,X/46,XY	Turner phenotype but streak gonads contain some Y cells
Ovo-testicular DSD	46,XX/46,XY	Testis + ovary
	46,XX	Testis + ovotestis
	Intra-gonadal mosaicism	Ovotestis + ovotestis Ovary + ovotestis
Pure gonadal dysgenesis	46,XY	Streak gonads and female internal ducts
PMDS	46,XY	Testes plus both male and female ducts

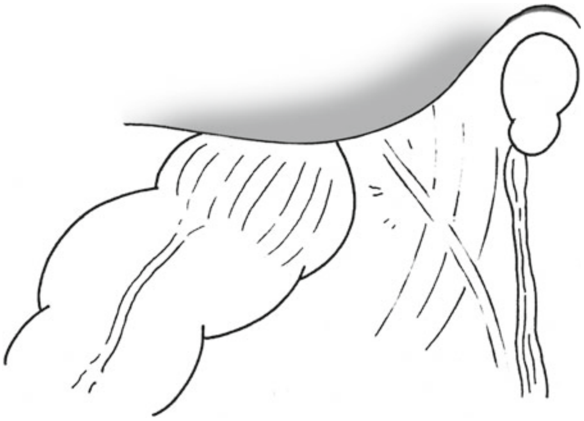

Fig. 18.1 Complete androgen insensitivity syndrome (CAIS) showing right intra-abdominal testis near the internal inguinal ring. Note the absence of Wolffian duct structures (epididymis and vas deferens), as well as Müllerian ducts behind the bladder

A small percentage of AIS patients have a less severe mutation of the androgen receptor, leading to partial insensitivity (PAIS) and external ambiguity because of partial virilisation. The Müllerian ducts are absent (as MIS/AMH is functioning normally), but only the proximal part of the Wolffian ducts are preserved (the epididymis and proximal vas deferens), where the concentration of hormone is sufficient to induce development, despite the abnormal receptor.

Laparoscopy is not always needed for diagnosis of CAIS, as the testis is usually found within the inguinal hernia and absence of the vas deferens confirms the diagnosis (Fig. 18.1). In female infants having laparoscopic herniotomy, the presence of testes but absence of the vasa deferentia, as well as absence of the uterus will indicate the anomaly. If the diagnosis has been made preoperatively (chromosome or testosterone analysis, pelvic ultrasound scan or rectal examination, which fails to find a cervix), then gonadectomy may be performed at herniotomy. Alternatively, where a testis is found unexpectedly in a hernial sac it is better to biopsy the gonads to confirm the diagnosis and replace them in the abdomen. Laparoscopy can be undertaken at a later date to perform bilateral gonadectomy, and confirm the internal genital anatomy. Many centres now recommend delaying gonadectomy until after puberty, as the malignancy risk is small (0.8%) and pubertal development can occur normally without hormone treatment.

In PAIS, laparoscopy may aid diagnosis, although the gonads usually are located in labio-scrotal folds, and the status of the internal anatomy can be confirmed by ultrasound scan or MRI.

18.3.2 45,X/46,XY Mixed Gonadal Dysgenesis (MGD)

In MGD the karyotype is commonly 45,X/46,XY, but other patterns have been described. The mosaicism usually is expressed to a different extent in each urogenital ridge, leading to gonadal and genital duct asymmetry (see Chap. 5). In the commonest variant, one gonad is testicular (with an accompanying vas deferens) and the other gonad is an undifferentiated streak gonad (with an adjacent Müllerian duct structure).

Laparoscopy is useful in MGD to confirm the internal anatomy, as well as remove one or other genital structures, depending on gender of rearing.

18.3.3 Ovo-Testicular DSD

The external genitalia often are asymmetrical and a number of chromosomal arrangements occur, although the commonest is 46,XX. In the latter situation, the peripheral blood is 46,XX, but there is a clone of 46,XY cells in the urogenital ridge or gonads.

Laparoscopy will reveal the retained ovary or ovotestis (Fig. 18.2) allowing a management plan to be formed. One of the common varieties shows an intra-

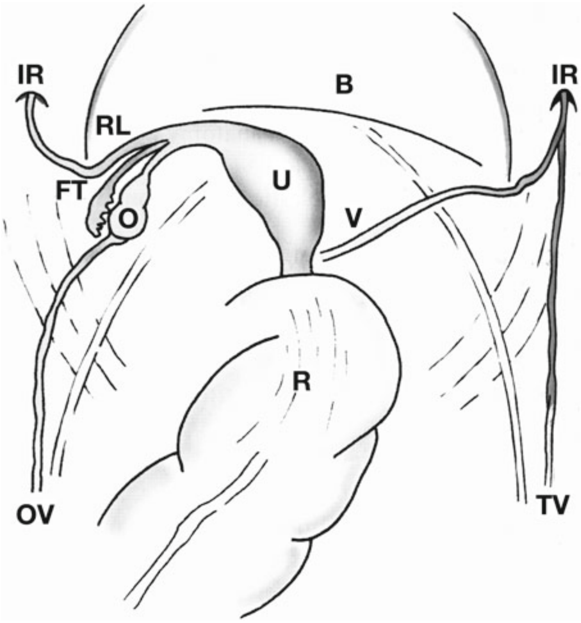

Fig. 18.2 Ovo-testicular DSD, showing one of the common varieties, with an intra-abdominal left ovary (*O*) and female genital tract [round ligament (*RL*); hemiuterus (*U*); fallopian tube (*FT*); ovarian vessels (*OV*)]. On the right side, the vas deferens (*V*) and gonadal vessels (*TV*) disappear through the internal inguinal ring (*IR*) to reach a descended testis. The bladder (*B*) is seen anteriorly and the rectum (*R*) posteriorly

abdominal left ovary and female genital tract (round ligament, hemi-uterus and tube and ovarian vessels). On the other side (often the right side) the vas deferens and gonadal vessels may disappear through the internal inguinal ring, connecting to a descended testis or ovo-testis. Gonadal excision or other procedure, such as orchidopexy, will depend on the gender chosen.

18.3.4 Pure Gonadal Dysgenesis (Swyer Syndrome)

These children usually present in adolescence with failure of pubertal development, as the appearance at birth is unambiguously female regardless of the genetic makeup. Gonadectomy is required for prevention of malignancy and puberty is induced by hormone treatment. The internal genitalia are feminine because of absence of testosterone and MIS/AMH, so pregnancy is potentially possible by IVF of a donor egg from a female relative (De Sutter 2001).

If laparoscopy is done during later childhood or adolescence (and prior to the commencement of oestrogen therapy) the uterine structure is likely to be very small. This structure can be missed by ultrasound if this is done at any time after the neonatal period when maternal oestrogens will be responsible for a more prominent uterus.

The ‘absent’ or rudimentary uterus on ultrasound and the very small uterus on laparoscopy has led to surgeons (and perhaps even gynaecologists) concluding that the uterus is absent. A simple vaginoscopy to confirm the presence of the cervix should be adequate reassurance. In the presence of an 46,XY karyotype, streak gonads and absence of any virilisation or oestrogenisation, then the diagnosis of pure gonadal dysgenesis is clear. The small uterus will respond to oestrogens and achieve a normal size and menstruate.

In view of the 3–5% rate of ectopic pregnancies in the context of in vitro fertilization with embryo transfer, there is an argument for removal of the fallopian tubes at the same time (Marcus and Brinsden 2002).

18.3.5 Persistent Müllerian Duct Syndrome (PMDS)

This rare form of genital anomaly presents with normal male external genitalia with either impalpable testes or a hernia ipsilateral to an impalpable testis (*hernia uteri inguinalis*). Endoscopy provides an excellent way of documenting the site of the gonads as well as identifying and/or removing the retained Müllerian ducts (hypoplastic uterus and Fallopian tubes). The hypoplastic vaginal cavity is usually left in situ, as the vasa deferentia drain into the vaginal vault.

18.3.6 Primary Amenorrhoea

Laparoscopy is sometimes advocated in the assessment of teenagers presenting with primary amenorrhoea. Prior to undertaking this procedure careful examination and simple investigations can almost always clarify the diagnosis of utero-vaginal agenesis.

Although laparoscopy is reported to be used in the context of diagnosing vaginal agenesis, the combination of primary amenorrhoea in the presence of normal secondary sexual characteristics, female reproductive hormones (FSH and oestrogens), karyotype and pelvic ultrasound with an absent uterus is more than adequate to make this diagnosis. The identification of non-cavitated uterine remnants is not important as they are not responsible for any future problems. Fimbria and part of the Fallopian tubes are often present either unilaterally or bilaterally.

18.3.7 Hypothalamic Hypogonadism

With this diagnosis, the young adolescent girl will present not only with primary amenorrhoea but also pubertal delay. There will be no evidence of virilisation or pubertal development. Hormonal investigations will reveal a very low FSH, LH and oestrogen. In this context, a pelvic ultrasound is likely to report an absent uterus or rudimentary uterus – when in fact it is very small. At laparoscopy the uterus may appear to be absent – to the inexperienced clinician – but fimbria, tubes, inactive ovaries and a small midline structure will be present. The uterus will respond to oestrogen and grow to a normal size, menstruate and will be able to carry a pregnancy.

18.4 Biopsy/Excision of Intra-abdominal Gonads

Gonadal biopsy should be performed in any situation where the diagnosis remains uncertain, despite all other investigations. Where the gonad is heterogeneous, the possibility of ovo-testicular DSD or secondary tumour (gonadoblastoma, dysgerminoma or malignant seminoma) should be considered, and multiple biopsies with frozen section may be needed. In ovo-testicular DSD, the gonad may contain adjacent ovarian and testicular tissue forming an ovo-testis – the ovarian tissue may be at one or both poles with testicular tissue between. To avoid missing the diagnosis, a longitudinal wedge biopsy should be taken.

Excision of gonads is required where there is gonadal tissue discordant with the gender of rearing, or Y-chromosome–containing intra-abdominal gonadal tissue. Undifferentiated streak gonads are excised easily, as their blood supply is very meagre and can be diathermied. More substantial gonads or gonadal tumours need formal ligation of the gonadal vessels first.

18.5 Excision of Internal Genital Ducts

Laparoscopic excision of genital ducts is required in DSD conditions with female internal ducts in a child being raised as a male (e.g. mixed gonadal dysgenesis and ovo-testicular DSD with unilateral Müllerian duct retention, and persisting Müllerian duct syndrome with bilateral duct retention), although delay in excision is recommended, if possible, until the gender identity of the individual is clear and consent by the individual can be given (see discussion in Chap. 7). Also, there are some males with androgenic dysfunction where there is a remnant of the urogenital sinus (primitive lower vagina). In children being raised as females, laparoscopic removal of Wolffian duct remnants may be required, as in some with ovo-testicular DSD.

18.6 Procedures

18.6.1 Pre-operative Preparation

Adequate pre-operative imaging and molecular diagnosis are the main pre-operative steps. Ultrasonography will determine the presence of a uterus or hemi-uterus in most cases, although MRI is useful if in doubt. It is important to remember that these structures will be quite small in the context of low oestrogens, beyond the early post-natal period. More important is the determination of the presence or absence of the urogenital sinus (remnant of the lower vagina) – retrograde urogenital sinugram (see Chap. 14) and/or urethroscopy are the best investigations. Where any uncertainty persists, urethroscopy at the start of the operation will resolve the issue. However, recognition and interpretation of normal anatomy and its variations require surgical and radiological expertise. The undiagnosed presence of a urine-storing lower vagina may seriously compromise subsequent hypospadias repair in DSD patients raised as boys.

18.6.2 Instruments

18.6.2.1 Essential

- Three 3.5–12 mm cannulae, with appropriate reducers as required
- 3.5 or 10 mm 30° angled telescope
- 3.5–5 mm curved insulated scissors with diathermy connection
- Two 3.5–5 mm atraumatic grasping forceps, one with a ratchet
- Fine 3.5–5 mm hook monopolar and bipolar diathermy
- 3.5–5 mm suction/irrigation device

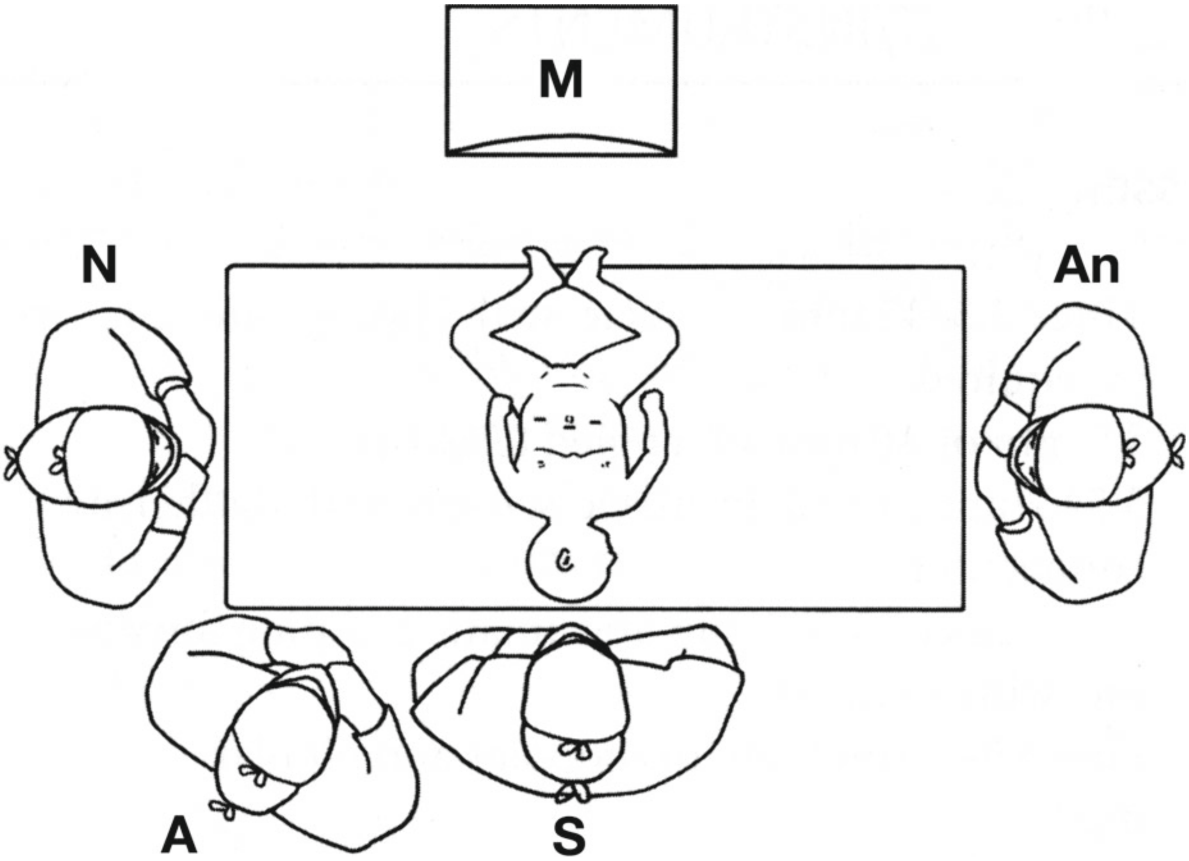

Fig. 18.3 Theatre layout for inspection/surgery of genital tract. The baby is across the table with the surgeon (*S*) facing the monitor screen (*M*). A low bar protects the baby's head and the anaesthetic equipment, with the anaesthetist (*AN*) to one side. The assistant (*A*) and nurse (*N*) are positioned to the other side. The relative position of the anaesthetist and nurse depends on the handedness of the surgeon. The sites of the ports are shown (umbilical telescope and lateral working ports)

- 5 mm clip applicator or endoloop sutures
- A 3.5 or 5 mm needle holder

18.6.2.2 Optional

- 3/0 or 4/0 atraumatic suture for trans-abdominal retraction of the bladder.

18.6.3 Technique

Under general anaesthesia, the patient is positioned supine. A pad under the buttocks often is helpful to elevate the pelvis. In babies a cross-table position is advantageous, with the lower legs dangling over the edge (Fig. 18.3). A crossbar over the head protects the anaesthetic apparatus and access to the airway by the anaesthetist, but allows the surgeon to stand at the patient's head. The relative positions of the anaesthetist and nurse depends on the handedness of the surgeon. The patient should be prepared with antiseptic to include the entire abdomen and genitalia, as well as the upper thighs. Passage of a urinary catheter ensures the bladder is completely empty.

A supra-umbilical incision and Hasson technique (open technique laparoscopy) allow insertion of the telescope (primary) port and introduction of the pneumoperitoneum. Two working ports are established, one on each side of the umbilicus. In babies, they are better placed higher in the epigastrium, although in older patients this is not needed.

To explore the pelvic viscera, the table should be tilted to place the baby in the Trendelenburg (head-down) position. If the pelvic organs are obscured by the bladder, this can be lifted out of the way by a trans-abdominal suture passed through the lower abdomen, picking up the back of the bladder, and then passed back out through the abdominal wall for traction (Fig. 18.4).

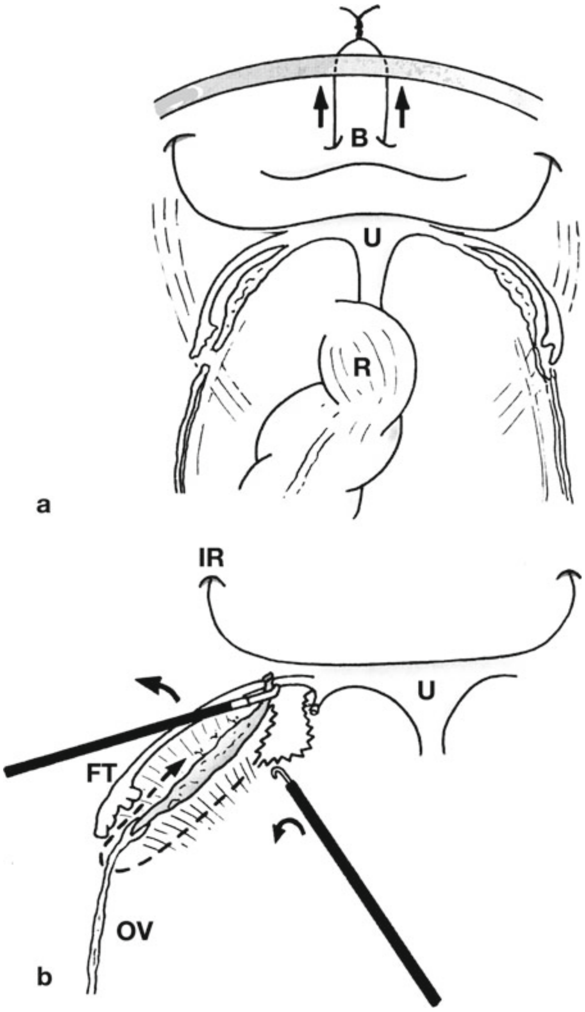

Fig. 18.4 (**a**) A trans-abdominal suture has been passed through the lower abdomen and picked up the back of the bladder (*B*) to expose the genitalia. In this patient the round ligaments, Fallopian tubes, uterus (*U*) and streak gonads are visible. This picture is seen in Turner syndrome with mosaic 45,X/46,XY chromosomes and in pure gonadal dysgenesis (46,XY) (**b**) Grasping forceps hold the infantile uterus (*U*) to expose the streak gonads (*S*). A second grasper holds the streak gonad while hook diathermy dissects it free from the back of the broad ligament. Dissection almost complete, except for the gonadal vessels. These are usually hypoplastic and can be diathermied. If in doubt, a clip or endoloop can be used

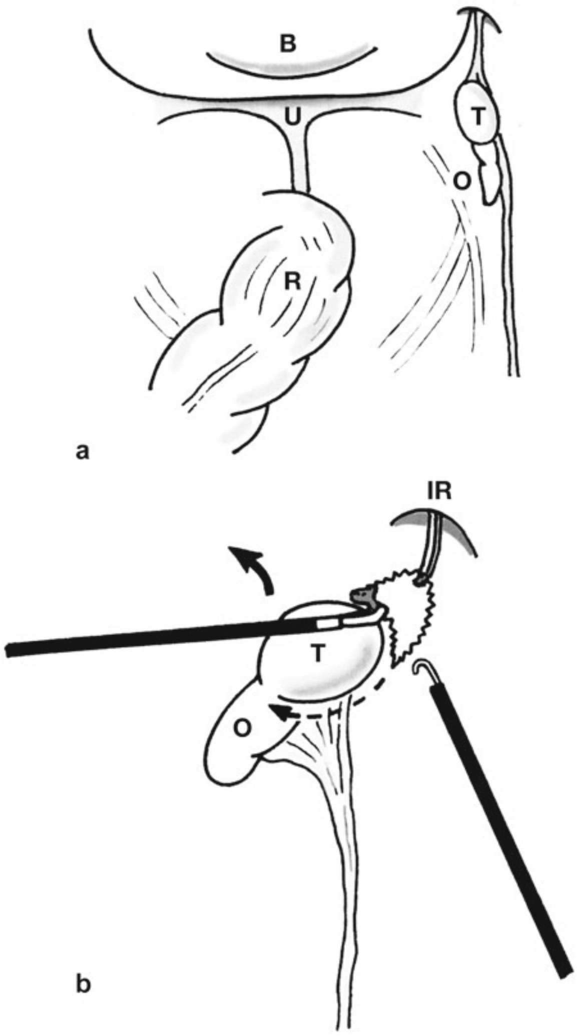

Fig. 18.5 (**a**) An ovo-testis has been identified on the right side after pulling the gonad back into the abdomen from the internal inguinal ring (*IR*). One pole of the gonad has a spherical testicular (*T*) appearance, while the other pole appears ovarian (*O*). The adjacent Fallopian tube (*F*) is hypoplastic. (**b**) Partial gonadectomy is being performed with hook diathermy, as the distinction between testis and ovary is obvious. If not, complete gonadectomy is a safer course

Inspection of the internal genitalia will reveal whether a streak gonad or ovo-testis is present and the status of the genital ducts.

If a uterus is present, this is picked up at the fundus with the grasping forceps to reveal the relative positions of the streak gonad and primitive Fallopian tube (Fig. 18.4).

A streak gonad is located close to the Fallopian tube with its medial and lateral ends almost inseparable from the uterus and fimbriated end of the tube, respectively. The gonad can be grasped with the other instrument – a ratchet allows the position to be maintained. Excision of a streak gonad can be performed with diathermy hook, scissors and diathermy, or bipolar diathermy. Clips or sutures often are not needed for the gonadal vessels as these are usually hypoplastic. If in doubt a clip or endoloop can be used. One must take care not to damage the uterus and its vessels medially, Fallopian tube anteriorly and the fimbriated end and ureter laterally (although with modern IVF techniques the tubes are not necessary, and may be removed).

For removal of streak gonads in girls with mosaic 45,X/46,XY Turner syndrome (which contain a Y chromosome), the Fallopian tube may be preserved to allow the maximum flexibility for subsequent assisted reproduction.

If an ovo-testis is identified with adequate distinction between the ovarian and testicular tissue, (one pole of the gonad has a spherical testicular appearance, while the other pole appears ovarian) then a hemi-gonadectomy is possible. A right ovo-testis with a left ovary is a relatively common circumstance in patients with ovo-testicular DSD. Excision of the testicular half of the gonad is straightforward (Fig. 18.5).

Where testicular tissue is present, the gonad is likely to partially descend through the internal inguinal ring. Traction on the vessels and internal ducts delivers the gonad back into the peritoneal cavity. Partial or total unilateral gonadectomy is carried out using fine hook diathermy, depending on the degree of delineation. If any doubt, complete gonadectomy is a safer course.

In persistent Müllerian duct syndrome, both testes may be intra-abdominal (Fig. 18.6a), or one (or both) testes may be prolapsed through the internal inguinal ring; if so, the testes should be pulled back into the abdomen, which is easy, as they are not attached tightly to the scrotum by the gubernaculum. The hypoplastic uterus and tubes are in a floppy broad ligament, which also encloses the vasa deferentia. The latter ducts run across the ligament to the lower end of the infantile uterus and then merge into the wall. Excision of the female genital tract, therefore, should only include the Fallopian tubes and upper uterus, and the cervix and hypoplastic vagina should be left in situ.

Traction on the Fallopian tubes allows diathermy hook dissection through the broad ligament, sticking close to the Müllerian duct structures (Fig. 18.7b). The lower part of the uterine body is amputated just above the site of fusion with the vasa deferentia. An endoloop or single transfixion suture can be applied to seal the uterine cavity. Orchidopexy now can be carried out, with the testes brought down through the same or separate canals, depending on the mobility. Usually, the length of the vas deferens is adequate to reach the scrotum, although sometimes the proximity of the two testes to each other prevents orchidopexy independently on each side. Where the testes are close together, the scrotum can be opened in the midline to create a pocket on each side. A grasping forceps is passed up to and through the inguinal canal, entering the abdomen on the medial side of the inferior epigastric vessels, and

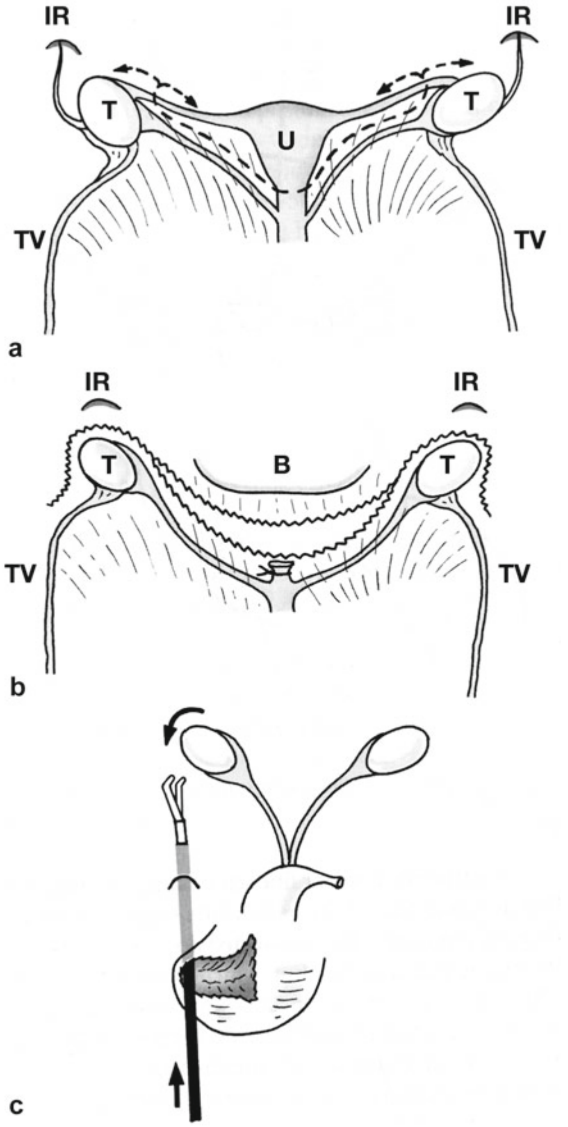

Fig. 18.6 (**a**) Persistent Müllerian duct syndrome with intra-abdominal testes (*T*) and a hypoplastic uterus (*U*). The broad ligament is usually long and thin, allowing much greater mobility than in the female. (**b**) Excision of the Müllerian duct structures in persistent Müllerian duct syndrome. Traction of the Müllerian ducts has allowed hook diathermy dissection of the broad ligament, staying close to the uterus (*U*). Transection of the lower-mid uterine body just above the level where the vasa deferentia merge with the uterine muscle. An endoloop has been applied to the uterine stump. (**c**) Creation of bilateral subcutaneous pouches in the scrotum via a small midline incision. Passage of a grasper up through the external inguinal ring from the scrotum. After dilating up the tunnel, the grasper takes hold of the testes. The abdomen may be entered medial (as shown) or lateral to the inferior epigastric vessels

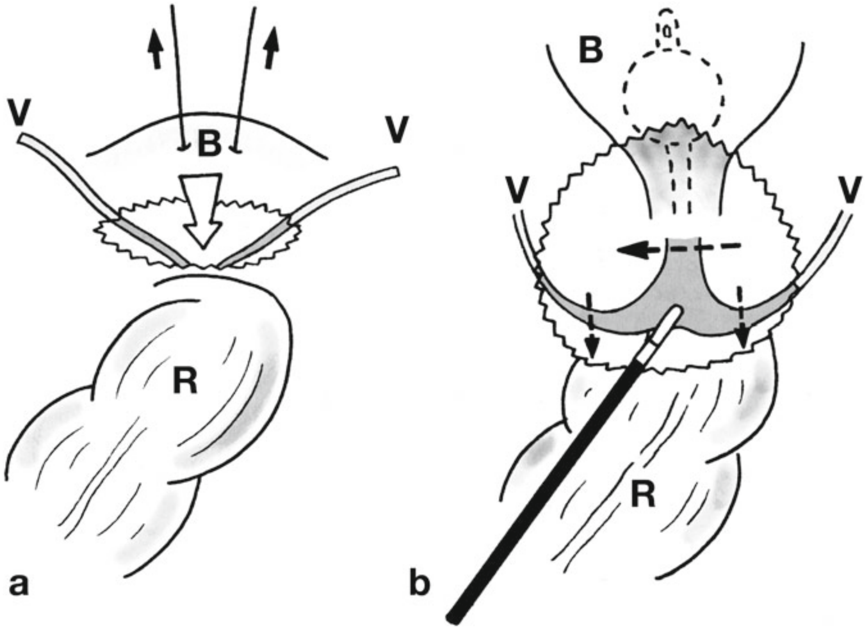

Fig. 18.7 (**a**) The peritoneum is opened low down behind the base of the bladder to expose the vasa deferentia. (**b**) Tracing each vas downwards reveals the connection to the vaginal remnant, which is dissected free from adjacent tissues down to its connection with the posterior urethra. A catheter or metal sound should be in the urethra. The vasa are divided with diathermy or scissors, and if epididymitis has occurred, the ipsilateral, dilated vas deferens is excised at the internal ring and the distal end is clipped or closed with an endoloop. Another endoloop closes the vagina where it attaches to the posterior urethra

both testes pulled down to the scrotum, once the track has been dilated. The testes then are positioned on either side of the scrotal septum.

In some boys with gonadal dysgenesis, there is a residual remnant of the lower vagina (derived from the persisting urogenital sinus). The vas deferens usually drains into the vault of the cavity, creating a conical or V-shaped structure. The peritoneum is opened transversely behind the bladder using diathermy hook or fine scissors, and the vasa deferentia are dissected off the back of the bladder to expose the vaginal remnant. This is dissected down to its connection with the posterior urethra, which is identified by the presence of a catheter or metal sound (or cystoscopy). Excision of the vagina requires transection of the vas deferens, which can be done at any convenient level, and then an endoloop or single suture ligation used to close the lower vagina at its entry-point into the posterior urethra. The vasa deferentia are divided with diathermy or scissors. If epididymitis has developed, the ipsilateral dilated vas deferens is excised at the internal inguinal ring, and its distal end is clipped or closed with an endoloop/suture ligature (Fig. 18.7).

18.6.4 Postoperative Management

Local anaesthetic in the port sites, plus some oral or narcotic analgesia for the first 12–24 h postoperatively, is usually adequate. Diet and fluids can be resumed immediately. If dissection has included extraperitoneal exposure of the bladder neck and posterior urethra, then a urinary catheter should be left in situ for a short while (12–24 h). Discharge home should be possible after catheter removal the next day.

18.7 Problems/Pitfalls and Solutions

The most frequent problem is likely to be confusion about the anatomy, because of the possibility of variable male and female structures. This can be avoided by careful pre-operative planning. Biopsy and photography and termination of the operation will allow the diagnosis to be made correctly.

18.7.1 Difficult Access or Poor View

1. Ensure Trendelenburg position and that the bladder is empty.
2. Use a trans-abdominal traction suture on the bladder if it is flopping down and obscuring the retrovesical structures. Alternatively, insert an extra port to enable the assistant to hold the back wall of the bladder up.

18.7.2 Bleeding

- This is rarely a major problem as the gonadal and uterine vessels are often small because of the poor development of the structures. If bleeding occurs, proximal occlusion of the gonadal vessels with grasping forceps will usually control it, or clips, suture or diathermy can be used.

18.7.3 Dissection behind Bladder Neck/Urethra

- ‘Tenting’ up the urethra by traction on the vaginal remnant may risk damage to the sphincter or create a fistula. Use of a stiff urethral catheter or a metal sound in the urethra will ensure this is not included in the dissection or excision margin. Alternatively, a cystoscope can be passed by an assistant to positively identify the junction between the urinary and genital tracts.

18.8 Complications

1. Inadequate gonadal excision, leaving potentially malignant streak gonadal tissue; or residual gonadal tissue from the opposite sex. Careful review of the biopsy/excised material, along with post-operative hormonal assessment (if needed) should determine whether repeat excision is required.
2. Incorrect excision of gonadal/ductal tissues. This can be avoided by not proceeding unless the surgeon is absolutely sure of the diagnosis and the state of the anatomy. Biopsy, photography/video recording and termination of the procedure until further advice is sought are reliable ways to avoid this disaster.
3. Incomplete excision of the vaginal remnant may lead to recurrent/persisting urosepsis, breakdown of the vaginal closure and retrovesical abscess. Avoid this by very careful positioning of endoloop (or clips) at the urethra–vagina junction.
4. Persisting epididymitis following retrograde spread of organisms may require a course of post-operative antibiotics. If epididymitis occurred pre-operatively, the ipsilateral vas deferens is usually dilated and/or inflamed, and this should be excised at the internal ring and the distal end closed with a clip or endoloop.
5. Posterior urethral fistula or sphincter damage can be avoided by keeping the dissection close to the wall of the vaginal remnant, and keeping a metal sound in the urethra. The assistant or nurse can manipulate the sound while the surgeon observes the posterior urethra or passes a cystoscope, to ensure that the dissection finishes at the correct point.
6. Potential injury to adjacent pelvic structures, particularly iliac vessels and ureter, can be avoided by careful instrumentation and dissection.

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The Family

19

Elizabeth Loughlin

What is the optimal psycho-social counselling service for families of an infant with uncertain sex?

What type of psycho-social counselling service can best assist families of an infant of uncertain sex? Psycho-social care is an essential part of the work of multi-disciplinary DSD teams (Parisi et al. 2007; Ahmed and Rodie 2010; Brain et al. 2010). This chapter presents a psycho-social counselling service based on a structured interview of parents with a DSD infant (0–3 years of age) and provides a description for its use. The second part of the chapter presents findings of a clinical audit of this structured interview that give more information about other characteristics and family issues. The results affirm key family issues, namely the delay in deciding gender, and the need to retell or delay gender as stressors for a proportion of parents in the cohort. Follow-on clinical counselling points to family concerns at different child developmental stages.

19.1 Background

As the social worker in the Endocrine Unit at the Royal Children's Hospital and a member of the DSD treatment team, the author has worked for over 20 years with families with an infant, child, adolescent or young adult with a range of DSD conditions.

The DSD paediatric team comprises endocrinologists, surgeons, gynaecologists, psychotherapist/Lacanian analyst (for some years), social work counsellor, hospital ethicist and consulting psychiatrist, along with visiting other members. Monthly meetings discuss clinical and ethical concerns of new and re-current referrals, recent research and clinical literature and the implementation of legal processes for decisions on genital or gonadal surgery. Full explanation of diagnoses and treatment to parents and to children and adolescents at appropriate developmental stages has been the policy during this time. Liaison with parent or patient support groups has been strong in the Department of Endocrinology and Diabetes and the Department of Social Work.

19.2 The Infant

The majority of DSD conditions present in the labour ward at birth when the doctor observes that the infant's genital anatomy is not clear, and organises investigations to determine the infant's sex. Parents' disbelief and resulting distress on hearing of their infant's unusual condition needs to be addressed, not only with information but with psycho-social counselling.

The birth scenario is a varying experience that is not anticipated nor easily controlled. The birth may take place in a city maternity hospital, where the doctors immediately transfer the baby to a paediatric tertiary centre. There, the DSD specialist team can provide clear discussion of a possible diagnosis. By contrast, the infant may be born in a small rural hospital, with a low incidence of such births, and with likely delays in providing clear information for parents. Parents themselves vary in their response to the infant's appearance depending on their personal capacities to cope with the unexpected and unknown, and also if they are vulnerable from significant prior losses and griefs. The timing

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of the birth notification varies; some parents have several days following delivery to learn about the diagnosis together; for other parents, the arrival of the new baby is known, and the early news they give about the baby may be incorrect, delayed or confused.

In the first few days at the paediatric tertiary centre, the parents learn much information about their infant's condition and treatment. In addition, with assistance of the doctors, the parents are expected to make informed decisions about the sex of their infant. Also within a short time span, parents are asked to think about the decision of surgery for their infant (Sanders et al. 2007). The decision is not made easily when there are differing views about infant surgery coming from adult patients and parent-support groups, and varying outcomes reported in the online medical literature, as well as a range of perspectives within the family's medical advisors.

The question is: What psycho-social service can best assist parents to (1) recover from the emotional stress at birth, (2) help them to become aware of information and decision-making about DSD conditions and (3) work out ways to tell relatives and friends about their infant's condition and possible change of gender, all in the short time the family is in the cloistered supportive setting of the hospital.

19.3 The Structured Interview

The structured interview for parents with an infant (0–3 years) with unclear sex was devised by the author in 2002, based on clinical experience of talking with families, and a video of remembered experiences of parents with older or adult children (Sahhar and Warne 1989). The framework consists of two semi-structured interviews of 45–90 min, covering 38 items. It developed from the need for a systematic assessment of stressors in families of a child with a chronic condition (Burke et al. 1999) and the links between parenting and attachment among toddlers with congenital anomalies (Clements and Barnett 2002). The framework was trialled over 12 months and additional items were added. Feedback on the draft framework was given by the medical team.

The structure was designed:

- To prompt the social work counsellor to cover all important issues and facts
- To offer the parents emotional and social counselling around their experiences after the birth of their infant
- To maintain a focus on the infant as the parents' new baby
- To make a broad assessment of the family adaptation
- And to provide audit information about family characteristics and family issues for the clinical DSD cohort

19.3.1 Use

The Assessment and Interview Framework lists items to follow in a natural order of importance under clear headings, but items may be covered in another order. Facts and dilemmas raised in the first interview can take the entire second interview to talk through fully (Fig. 19.1). Further interviews are offered if parental distress continues or if the infant is ill.

Each item is answered from three information sources – parent report, social work observation and verbal report of other team members or documentation in the patient's medical file. Some items (1–8) are experiential items, for example, item 1: Parents' response to unclear genital appearance; item 2: Mother's response shortly after birth. Other items, for example, item 12, Sex of baby decided, are facts. Each item in the framework has sub-categories, for example, yes/no/NK, with one sub-category to be circled.

Some items provide opportunity for more discussion. Items 1–8, for example, about the events at birth, allow parents to go slowly through what has happened to them and their infant in a personal sense. There is opportunity for open questions about what actually happened, who said what, what was felt, what did they see of the infant's appearance and when. If the family says that everything is clear and they are not worried about the condition, it is still important to talk through the items for educative purposes. Item 10 is about the quality of the birth, which is a possible additional stressor that may need to be talked through. Item 11 includes the few families where the infant has unclear genitalia and also multiple medical problems, which may be of more concern to the family in the beginning, especially if there are survival issues.

Items 14 and 15 about 'Diagnosis' are an opportunity to ask the parents what they have understood so far and what they are deciding with regard to decision on gender and also later surgery. Parents can be overwhelmed with the speed of medical investigations, as well as the delay in the medical answers. Parents may

Events surrounding the birth and ensuing days of investigations and decisions

1. Parents' response to ambiguous genitalia: adapted/ distressed/ traumatised/ not known (NK)
2. Mother's response shortly after birth: adapted/ distressed/ traumatised/ NK
3. Decision on gender at day 1 or 2: clear/dilemma/ delayed/NK
4. Decision on gender by day: 0-2/3-7/8-14/15-30/>30/NK
5. Need to retell or delay gender to kin: yes/ no/ NK
6. Need to retell or delay gender to friends, community: yes/ no/ NK
7. Medical management (including clinical reports): clear/ unclear/ NK
8. Medical management (parents' perceptions): clear/ unclear/ NK

Infant

9. DOB Infant: …..
10. Birth: normal/ unexpected difficulties/ traumatic/ NK
11. Infant parallel serious health condition: yes/ no
12. Sex of baby decided: male/ female
13. Infant subsequently alive/deceased

Diagnosis

14. Diagnosis: CAH, CAIS, PAIS, MGD, ovotesticular DSD, Severe hypospadias, Klinefelter, other atypical genital appearance; other
15. Medical diagnosis at day: 0-2/3-7/8-14/15-30/>30/NK

Pre-existing issues

16. Pre-existing issues with infertility, miscarriage, neonatal loss or other loss that has impacted on self concept or parent relationship: yes/ no/ NK
17. Pre-existing long-term problems of mother's or father's family: yes/ no/ NK

Cultural

18. Cultural background: English or Northern European/ Mediterranean/ Asian/ Muslim/ Indigenous & Islander
19. Residence: Victorian (Home state of hospital) metropolitan or rural city/ Victorian rural or small country town/ Interstate or interstate rural/ New Zealand and overseas

Emotional supports

20. Mother feels supported post-natally by partner, close family member: yes/ somewhat/ no/ NK
21. Maternal grandmother supportive and nearby: yes/ somewhat/ no/ NK

Parent–infant relationship

22. Mother, father observed attached to baby: yes/ developing/ no/ NK
23. Parental cultural preference or strong expectation for male or female: no preference/ boy/ girl/ acted on/ NK

Engagement

24. Parents engaged with psycho-social counselling, social work (2 interviews 45–90 minutes : yes/ somewhat/ no
25. Mother, father engaged with medical investigations with discussion of options for surgery, and possibility of some uncertainty in DSD outcomes: yes / no/ NK

Follow up

26. Interested in psychosocial counselling (outpatient or phone) (ie recognition that they are experiencing huge adjustment, and infant will also): yes/ somewhat/ no/ NK
27. Willing to listen to existence of support groups and their style of support, even if do not want contact at present time: yes/ somewhat/ no/ NK
28. Acceptance that professional review –Medical specialist, Maternal Child Health nurse and other health personnel - is implicit in diagnosis

Service details

29. Referral day for psychosocial counselling: 0–2/3–5/6–15/ 16–90/3–6 months/1–2yr/>2–5yr
30. Referred by Surgeon/ Senior Endocrinologist/ Gynaecologist/ Endocrinologist 1/ 2/ 3/ Other
31. Date first seen by social worker……
32. Where first seen by social worker: ward /outpatients / maternity hospital/ telephone/ missing
33. Second interview conducted: yes/ no
34. Date social work second interview interview……..
35. Where social work second interview: ward/ outpatients/ maternity hospital/ telephone/ support group newsletter mailed/ letter/ missing
36. Social worker (SW): Endocrinology SW/ Neonate SW/ Neonate & Endo SW/ Other SW
37. Further extra follow-up clinically indicated: yes/ no
38. Individual SW comment about family: yes/ no

Comments 1, 2, 3, 4 Individual family characteristics

Fig. 19.1 The Social work assessment and interview framework of 38 items

require a mental space to pause, take stock, begin to feel in control and integrate what is happening each day. Some parents have remarked of the psycho-social interview with comments such as, 'This is the interview we needed to have – to sort out who is who and what will happen'.

Item 25, about parental engagement in investigations and options for surgery and the possibility of prognostic uncertainties can lead to brief or more wide-ranging discussion. This is reflected in comments like, 'We have decided to do the surgery after thinking a lot, and we can tell our daughter we did what we thought was the right thing at the time'. There may be comments such as, 'We'll accept the partner our child chooses – we just want him to grow up and be happy'.

Items about previous stressors (16 and 17), for example, infertility, miscarriage, stillbirth or other loss. Ask first about the pregnancy: was the mother well, was it planned or unexpected or occurred through assisted reproduction. Wider family relationships naturally emerge with items 5 and 6 about telling or retelling the gender of their baby to others. Item 20, about whether mother feels supported post-natally by partner or close family member, is a prompt to observe the parental relationship and capacity for mutual support during the interview. Most interviews are with both parents or the one parent explains why the second parent is not present. Item 27, about willingness to discuss support groups and their style of support, even if they do not want contact at that time, is an opportunity to explain and provide helpful internet resources for families. The following are some useful ones: http://www.dsdguidelines.org, or for caregivers and adolescents http://www.sickkids.ca/childphysiology/cpwp/Genital/genitaldevelopment.htm. Items 37 and 38 are based on the counsellor's assessment of the family and the need for follow-up, with space for individual comments about particular family issues.

If the mother has unabated distress or depression, this triggers referral to the consulting hospital psychiatrist, family doctor or to the maternal child health nurse to avert or treat post-natal depression and anxiety.

19.3.2 Announcing the Infant's Birth to Others

As the medical issues become clearer for parents the dilemma of how to explain their infant's condition, and if necessary, how to delay or retell the gender to relatives and friends becomes insistent and perplexing. Secrecy surrounding the birth of an infant with different genital appearance has now become an issue of who and what to tell. Items 5 and 6 are an opportunity to assist parents to think about how to tell relatives and friends and yet preserve what they feel is right for their infant, their future child/adolescent's body image and self image. Parents want to rely on their own siblings and close friends for emotional support and yet want to keep the confidences about their baby – who cannot give permission – to a trusted few. Some families may choose to gather all the relatives to talk about the condition at the same time; others may decide to explain the details of the condition to only one set of grandparents. In country towns where families share local doctors, parents can be more cautious than city families about who they tell. While published American guidelines for parents (www.dsdguidelines.org) encourage straightforward explanation of their child's DSD to relatives and friends, in Australia there is more reserve in communicating sensitive matters about family members. Young women with a DSD, who attended the gynaecology clinic groups, have said they were aware of whom their mother 'told' without their 'permission'. Families of South-East Asian background (Warne and Bhatia, 2006) often wish to keep to their own cultural rules in communicating the DSD condition to others.

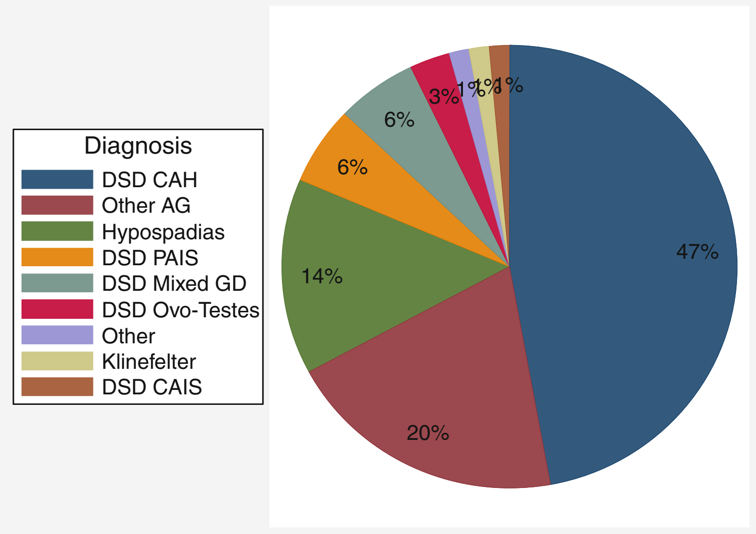
Discussion with parents to devise their own strategies may include the following: (1) Decisions on who to tell and what to say differently to close family, to friends, to neighbours and to acquaintances. (2) Thoughts of what the future adolescent would wish parents to say. (3) Requests to doctors for full information about the condition so parents feel confident to speak to others on a variety of levels. It is important to encourage parents to be firm when others ask what is wrong or if others are just curious, and remind them that when they speak with confidence other people are reassured.

From the author's perspective the items most powerful for parental confidence are items 1, 5 and 25. In item 1, parents name the very difficult situations that can arise at the birth. In item 5, where there may be a need to delay or retell gender, the parents do joint work to establish a new distance or closeness with relatives and friends. Thirdly, in item 25, most parents begin to anticipate their baby in the future as a healthy competent young person.

19.4 The Audit Study

A clinical audit of the use of this structured interview was conducted with 70 families over a period of 5.5 years from July 2002 to January 2009. This provided new and systematic information about family

Fig. 19.2 Diagnosis



characteristics, family issues and also quality assurance information. The audit was approved by the hospital ethics committee. Families with an infant without genital ambiguity, for example those with Turner Syndrome, were not part of the audit cohort.

19.5 Method

Answers to the Framework items as variables were entered into the Epidata software data-base. The subcategory 'not known' informed how many in the cohort were either not asked about the item/variable or were not remembered by parents, often due to later presentation of the infant.

The STATA 11 statistical program was used to obtain descriptive frequencies and cross tabulation of variables. The levels of significance were obtained with Pearson Chi^2 and Fisher's exact. In cross-tabulation of variables the sub-category 'not known' was taken out and cohort number noted. The sub-categories of several variables were collapsed for the purpose of analysis; variable 1 [Parents' response to unclear genital appearance: adapted/distressed/traumatised] was collapsed to distressed or traumatised: no/yes; and variable 14, [Diagnosis with nine sub-categories] (Fig. 19.2) was collapsed to four Diagnostic Categories: with four sub-categories, (1) CAH; (2) DSD that required more decision-making: CAIS, PAIS, MGD and Ovo-testes; (3) Severe hypospadias and (4) other DSD (Fig. 19.3).

19.6 Findings

There were 25 males and 45 females in the infant cohort, ($n = 70$) with 66 alive and 4 deaths. Parallel health issues were present in 23/70 families, and 21 had unexpected difficulties or trauma at delivery. There was a wide spread of referral day for psycho-social counselling, with 11 within 2 days of delivery and 11 more by 5 days. Fourteen were referred between 2 weeks and 6 months and 30 thereafter, the latter reflecting the number of families from interstate and overseas.

As shown in Fig. 19.3, the largest group of DSD was CAH followed by DSD conditions that involve careful decision-making about sex (CAIS, PAIS, MGD and ovo-testicular DSD), then severe hypospadias, where the genitalia were ambiguous and then other DSD conditions.

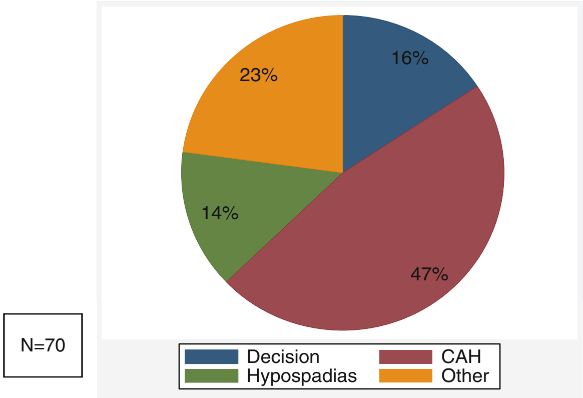
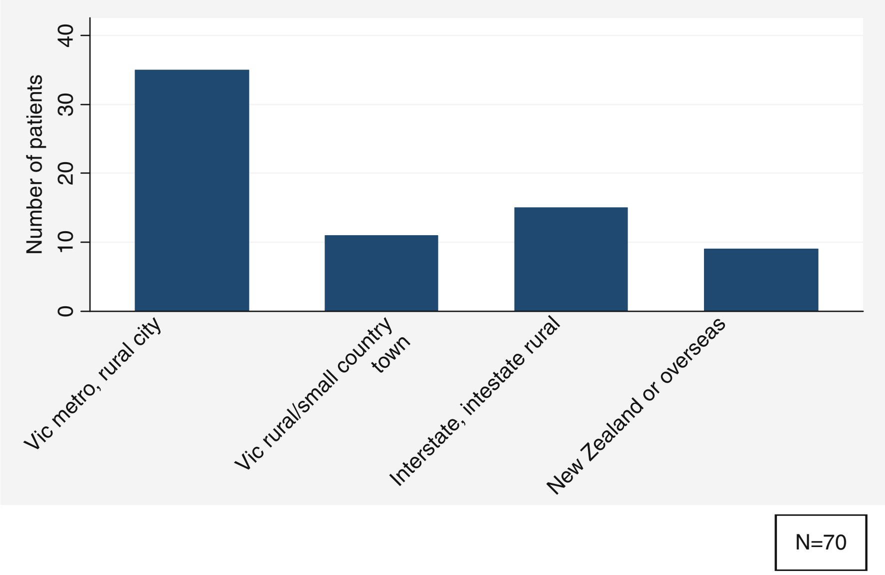


Fig. 19.3 Diagnoses in four categories

Fig. 19.4 Family residence



19.6.1 Family Residence and Cultural Background

The family residence is shown in Fig. 19.4, and reveals that about one-third of the families were from interstate or overseas. Cultural background was identified by parents: English or Northern European predominated at 55, (79%); Asian 5, (7%); Mediterranean 5, (7%); Indigenous or Islander 3, (4%); Muslim 2, (3%) (Arabic 1, African 1). Parent cultural preference or strong expectation for male or female infant (variable 23), showed no preference 69, (99%); not known 1, (1%).

19.6.2 Parent Characteristics

19.6.2.1 Adaptation

Parents in the cohort showed a range of adaptation, distress or trauma to the birth (variable 1). Half the parents reported or were observed at the time of interview to be adapting to the unclear genital appearance while 28 (40%) reported or were observed to express distress. Five families (7%) were still feeling traumatised, with (3%) unknown. Mother's response shortly after birth (variable 2) showed more distress and trauma than parents together (variable 1), with only 22 (31%) adapted.

19.6.2.2 Parent Pre-existing Issues

Issues surrounding infertility, miscarriage, neonatal loss or other loss (variable 16) were present in 11 families (16%), but in 25/70 (36%) it was not known.

19.6.2.3 Dealing with Uncertainties

The mother and/or father were observed to be engaged with medical investigations with discussion of options for surgery, and DSD outcomes (variable 25) in 59 families (84%). Many parents had the capacity to think about and tolerate some uncertainty in the future.

19.6.2.4 Parent–Infant Attachment

The mother and/or father were observed to be attached to the baby (variable 22) in 63 families (90%).

19.6.3 Family Issues

19.6.3.1 Decision Regarding the Gender at Day 1 or 2

The decision regarding gender at day 1 or 2 (variable 3): was clear in 30 families (43%), but there were problems in 36 (51%). Less than half the infants had a clear gender by the end of day 2. The following Tables 19.1 and 19.2 show a significant association between the parents' or the mother's response of adaptation to distress and trauma, and the decision about gender at day 1 or 2.

There was a need to retell or delay gender to kin-relatives (variable 5) in 27 families, 38.57%, and 21 families (30%) needed to retell or delay gender to friends and community (variable 6). Overall, more than a third of parents had to retell or delay the gender to kin, and somewhat less than a third to friends and community.

Table 19.1 Parental distress/trauma vs Decision on gender at day 1-2

Decision on gender at day 1 or 2	No	Yes	Total
Clear	21	8	29
Dilemma/delayed	12	24	36
Total	33	32	65

$n = 65$, $p = 0.006$

Table 19.2 Mother's response after birth vs Decision on gender of day 1-2

Decision re gender at day 1–2	Adapted	Distressed	Traumatized	Total
Clear	19	4	4	27
Dilemma/delayed	3	28	4	35
Total	22	32	8	62

$N + 62$, $p < 0.001$

Table 19.3 Parents' distress/trauma vs need to retell or delay gender to kin

Need to retell or delay gender to kin	No	Yes	Total
Yes	9	18	27
No	22	12	34
Total	31	30	61

$N = 61$, $p = 0.015$

Table 19.4 Mother's response after birth vs need to retell or delay gender to kin

Need to retell or delay gender to kin	Adapted	Distressed	Traumatised	Total
Yes	2	23	2	27
No	20	7	5	32
Total	22	30	7	59

$N = 59$, $p < 0.001$

Table 19.3 shows a mildly significant association for the parental response to unclear genital appearance with distress and trauma, and need to retell or delay gender to friends and community. Table 19.4 shows a significant association between the mother's response shortly after birth and the need to retell or delay gender to friends and community.

Cross-tabulation of parental distress and trauma, and need to retell or delay gender to friends and community was not associated at a significant level. By contrast, the mother's response shortly after birth and the need to retell or delay gender to friends and community was highly significant.

19.6.4 Other Selected Associations

Pre-existing issues of infertility, miscarriage or neonatal loss in the family were significantly associated with parental distress and trauma. Cultural background and residence were not significantly associated with parental distress and trauma. Whether the mother felt supported post-natally by father or close family was significantly associated with her response shortly after birth. However, whether the maternal grandmother was supportive and nearby was not associated with mothers' response shortly after birth, as clinical experience expected.

19.7 Discussion

Audit of the structured interview highlighted the parental characteristics to take into account during the psycho-social counselling interviews. The significant association of certain variables affirms family issues, namely the delay in deciding gender and need to retell or delay gender to relatives and friends as a stressor for parents. This indicates the need to address parent distress and work for parent adaptation in these areas.

Certain pre-existing issues are associated with parental distress/trauma as expected in families with a child with a serious health condition (Kazak et al 2003). Other variables such as residence and cultural background were not associated with parental distress and trauma as expected from clinical experience. It may be that the South-East Asian families' strong beliefs of not telling others about the DSD asks for more intensity and time in counselling and different ways to individualise the family engagement in the counselling.

Similarly, several families in rural areas have found others have spread rumours about their infant's DSD but these numbers were small and again need more clinical time and individualised counselling.

The association of the mothers' response shortly after birth to some variables described above, points to the vulnerability of the mother who has just given birth. Even so most parents (90%) were observed to have a positive attachment to their baby.

The associations presented indicate that the structured framework of evaluation is covering of important family stressors, family issues and other parent and infant information.

19.8 Issues for Families at Subsequent Counselling

Follow-up counselling for parents and young patients self-referred, or re-referred by doctors for problems, reveals parents' pre-occupations and family issues. Parents requested guidance about how to tell the young child aged 2–4 years about their DSD condition; or how to explain to the older child the unclear genital appearance of their sibling at birth. Parents worried about school-start for boys with hypospadias, and also feared at the secondary school level that the different appearance of the penis would affect their son's self-esteem, and lead to teasing or bullying from other boys. Families were referred for marital discord or parental separation when it was impacting on their adolescent's behaviour.

Some parents needed to go over the events post-birth again years later, which may reflect the depth of trauma they had experienced, even though their child was doing well. For girls with Turner Syndrome, now a DSD condition, some families worried over their girls' self concept, and ability to make friends, while their daughters wondered about future relationships and their infertility (Loughlin 2006).

The presence of the parents lessened when young women were referred to the paediatric transitional gynaecology clinic, which sees patients up to 24 years of age. In this clinic, issues are raised in individual and group psycho-social counselling about the physical loss of their sexual and reproductive structures, infertility and beginning sexual relations; occasionally, the psycho-social counsellor will see parents for supportive counselling where the young woman is diagnosed later in adolescence. Questions of gender identity were rare, but if present were referred to the consultant psychiatrist.

19.9 Implementation: Recommendations

What does the family need from the psycho-social services?

1. To be referred for psycho-social counselling and structured interview as soon as possible, ideally within a couple of days of hospital admission to cover all important family issues that are held in common, but with individualized counselling, particularly with regard to cultural responses to privacy in talking to others.
2. Follow-up counselling based on the framework items as an indicator of need, with review offered at 2–3 years. Further, non-medical preventative psycho-social work may be curtailed as funding for this purpose is not considered the task of the large crisis-oriented paediatric centre.
3. Discussion of pre-existing issues of prior infertility, assisted reproduction or pre- or neonatal loss may still be unresolved, and will need extra counselling to address old trauma in order to adapt to their infant's DSD condition.

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Genetic Counselling

20

David Amor

20.1 Introduction

Disorders of Sexual Development (DSDs) have a range of aetiologies, but for most DSDs genetic factors are prominent. As understanding of the genetic contributions increases, clinicians are increasingly faced with questions about why the DSD occurred and whether it will happen again. This chapter provides an overview of the process of genetic counselling, emphasising the elements most relevant to genetic counselling for DSDs, and then individual DSDs, summarising the specific aspects of genetic counselling for each condition.

20.2 Overview of Genetic Counselling

Genetic counselling is an important component of the management of DSD patients and their families, and may take place in a variety of clinical settings. Genetic counselling for DSDs frequently takes place within a multi-disciplinary team, and is typically carried out by clinical geneticists, genetic counsellors or by other health professionals with specific expertise in genetic counselling.

Genetic counselling for DSDs can take place at any stage of life, but most commonly occurs in one of four clinical contexts:

1. A couple with personal or family history of DSD planning a pregnancy
2. Prenatal diagnosis of DSD
3. Following diagnosis of DSD in a neonate or young child
4. An adolescent or young adult affected by DSD and seeking information about their own diagnosis

Genetic counselling is a complex process that is difficult to encapsulate in a single definition; however, the content and process of genetic counselling typically includes, to varying degrees, six main elements (Harper 2010), which are summarized below.

20.2.1 Diagnostic and Clinical Aspects

Genetic counselling depends on accurate diagnosis, and it is essential that the diagnosis be made as firm as possible before risk estimates are given. In addition to careful history and examination, additional data may be obtained from a variety of sources, such as interviewing multiple family members, seeking archived medical records, pathology reports and death certificates. In DSDs, a careful endocrine, chromosome and molecular assessment is necessary before accurate genetic counselling can be given. Once a diagnosis is confirmed, it is important that the counsellor understands the natural history of the DSD, and is able to communicate this to the patient and their family in a meaningful way.

20.2.2 Documentation of Family and Pedigree Information

The collection of family information is best achieved by drawing a family tree or pedigree. A clearly drawn pedigree provides a permanent record of genetic information

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in a particular family and conveys genetic information more clearly than other forms of family history documentation. Pedigrees drawn during the consultation also serve as a psycho-social tool, providing the opportunity to explore and better understand family dynamics and relationships. Careful inquiry may be required to elicit a family history of genital ambiguity, information about which may not have been widely communicated within the family. Information about family history of stillbirth, neonatal death and consanguinity should also be sought.

Special care is required when drawing pedigrees in DSD families. Symbols used in constructing pedigrees include male (□), female (○) and sex unknown (◊); in DSD families, the symbols for male and female should be used to denote sexual identity rather than chromosomal sex. Where known, chromosome sex can be included as an annotation.

Although many DSDs follow classical Mendelian inheritance, two points warrant emphasis. First, for X-linked recessive disorders that cause sex reversal (e.g. androgen insensitivity syndrome), the pedigree at first glance may not suggest X-linked inheritance because affected individuals are phenotypically female, rather than male. Second, there exist Mendelian DSDs that are penetrant for only one chromosomal sex; for these disorders, the phenotype may skip one or more generations, and the risk of having an affected child is half of the genetic risk.

20.2.3 Recognition of Inheritance Patterns and Risk Estimation

Once all available information has been collated, it should be possible to make a risk estimation. In the setting of DSDs, request for risk estimation usually take one of three forms:

1. Risk of having a second affected child
2. Risk of transmission from an affected parent to a child
3. Risk of having an affected child when a more distant relative is affected

Risk figures in genetic counselling can be given either as odds (e.g. ‘1 in 4’) or as percentages (e.g. 25%), with the method of explanation tailored to the needs of the client. For Mendelian disorders, an exact risk can be given on the basis of the known inheritance pattern, typically ranging from ‘negligible risk’ to 50% risk. For chromosome disorders and non-Mendelian disorders, risk estimation is usually empirical, based on observed data rather than theoretical predictions. The accuracy of empirical risk estimation depends on the quality of the available observed data, and the degree to which it matches the client’s personal situation. For very rare disorders, the only source of risk estimation might be from case reports of recurrence (or lack thereof).

20.2.4 Communication

Genetic concepts are typically complex, and need to be coupled with effective communication if genetic counselling is to be effective. Information about the psychological, emotional and practical impact of the diagnosis, genetic test results, natural history of the DSD and available treatments should be conveyed in way that is easily comprehensible, taking into account the scientific literacy of the family. Genetic counselling must also be sensitive to the sexual identity of those affected, and care must be taken to avoid assuming that chromosomal sex will necessarily determine sexual identity.

Most genetic counselling sessions are followed up by a letter in plain language to the client, summarising the main points discussed and documenting any risk estimate. Finally, although generally distinct from psychotherapeutic counselling, genetic counselling frequently has a therapeutic element, arising from the willingness of the counsellor to listen to and acknowledge the client’s experiences, the focus on the agenda of the client and the empathy shown during the consultation.

20.2.5 Information on Available Options

Many genetic counselling sessions result in the client being presented with choices. In DSD genetic counselling, choices frequently centre on reproductive options, but may also include decisions about whether to pursue further genetic testing and whether to pass on information to other family members.

20.2.6 Support in Decision Making and for Decisions Made

A key element underlying genetic counselling is nondirectiveness. In practice, this means that a goal of genetic counselling is to provide clients with the appropriate information to enable them to make their own informed decisions, taking into account the client's attitudes, perceptions and beliefs. The genetic counsellor may facilitate and support the client's decision-making, but should avoid advising the client on which choices to make. Finally, the genetic counsellor should assess the need for further counselling and follow-up.

20.3 Reproductive Options

For many DSDs, there is a significant risk of recurrence for siblings or offspring; following diagnosis of these DSDs, families are faced with difficult choices about future pregnancies. Reproductive choices are very personal, and not all options will be considered by all families. Where future pregnancies are at risk of DSD, there are six main reproductive options that may be available.

1. Accepting the risk of having another affected child.
2. Deciding not to have further children.
3. Pre-natal diagnosis and termination of pregnancy.
4. Pre-implantation genetic diagnosis (PGD).
5. Use of donor gametes or donor embryos.
6. Adoption.

For some individuals who are themselves affected by DSDs, reproduction using their own gametes will not be possible. For these patients, conception using donor gametes may be possible, and, provided the donor is not a genetic relative, the risk of recurrence will be avoided.

20.4 Prenatal Diagnosis

Some couples who are at increased risk of having a child with a DSD will elect to have prenatal diagnosis. Chorionic villus sampling (CVS) and amniocentesis can be used to obtain diagnostic samples that can be used for traditional cytogenetic analysis, chromosome microarray analysis and specific gene testing for monogenic disorders, where the family gene mutation is known. CVS testing allows first trimester diagnosis using foetal tissue obtained from chorionic villi, can be performed from 11 weeks' gestation, and carries a risk of miscarriage of ~1 in 100. In contrast, amniocentesis cannot be performed until 15 weeks' gestation, and carries a lower risk of miscarriage of ~1 in 200.

Foetal ultrasonography can provide additional prenatal diagnostic information. Ultrasound determination of foetal sex is unreliable prior to 12 weeks' gestation, but after 13 weeks' gestation is accurate in 99–100% of cases where genitalia are not malformed (Odeh et al. 2009). Genital ambiguity can also frequently be detected by ultrasound, but accuracy of diagnosis will depend on the severity of the malformation.

DSDs may also be diagnosed prenatally in pregnancies that have not previously been identified as being at increased risk. Chromosomal DSDs are frequently diagnosed at CVS or amniocentesis, either as an incidental finding in pregnancies that are being karyotyped because of increased risk of Down syndrome, or in the case of Turner syndrome, following the detection of ultrasound abnormalities such as nuchal oedema or cardiac malformation. Genital ambiguity at prenatal ultrasound may also be the presenting finding. The differential diagnosis for this presentation is broad, and should trigger further investigation including karyotype, FISH for SRY and careful ultrasound search for additional structural abnormalities (Pajkrt et al. 2008). In a 46,XX foetus, the most likely diagnosis is congenital adrenal hyperplasia, whereas in a 46,XY foetus the differential diagnosis is broader and includes androgen insensitivity syndrome, 46,XY gonadal dysgenesis, testosterone biosynthesis defects, and rare syndromes such as Smith-Lemli-Opitz syndrome and campomelic dysplasia. Ambiguous genitalia may be accompanied by a number of other ultrasound abnormalities, including abnormalities of the urinary system, and are associated with a number of chromosome disorders. Finally, the presenting finding may be discordance between chromosome sex at CVS/amniocentesis and the appearance of genitalia on prenatal ultrasound. Such discordance may indicate the diagnosis of a DSD such as AIS (Bianca et al. 2009) or gonadal dysgenesis (Mazza et al. 2003).

20.5 Pre-implantation Genetic Diagnosis (PGD)

PGD was developed for couples at high risk of having a child with a genetic disorder, as an alternative to prenatal diagnosis and selective abortion. The number of PGD tests performed each year is rising, resulting in more than 4,000 children born since the early 1990s (Goossens et al. 2009). PGD commences with couples undergoing IVF treatment, using standard procedures to collect oocytes through ovarian hyper-stimulation, followed by IVF techniques such as intra-cytoplasmic sperm injection (ICSI) and in vitro embryo culture. Embryos are most commonly biopsied on day 3 after fertilization, at which stage the embryo comprises six or more cells. For the diagnosis of single gene disorders, biopsied cells are tested for DNA mutations using DNA fragments that have been amplified by PCR. Detection of chromosome aneuploidy and unbalanced chromosome rearrangements, as well as selection of chromosomal sex can be accomplished using fluorescence in situ hybridization (FISH) or microarray analysis. Following successful diagnosis of the embryos, unaffected embryos are either transferred into the womb or frozen for possible future use. Approximately 25% of embryos transferred result in a clinical pregnancy.

A PGD test can be designed for virtually any inherited monogenic disorder or chromosome disorder, including many DSDs, and PGD has been reported for congenital adrenal hyperplasia (van Rij et al. 2011) and androgen insensitivity syndrome (Harper et al. 2010). Although PGD is an attractive option for many families because it avoids the need to consider termination of pregnancies, the relatively high cost precludes some families from accessing the technology.

20.6 Genetic Testing

Genetic testing is now a routine part of clinical practice and plays a key role in management of DSDs, for which genetic testing falls into two categories: cytogenetic analysis and molecular mutation analysis.

20.6.1 Cytogenetics

Cytogenetic analysis, and particularly information about the sex chromosomes, is a key part of the diagnostic process of DSDs, and is the only way to accurately diagnose chromosome DSDs. Standard microscope karyotype should be performed in all cases, with at least 30 cells examined in order to exclude mosaicism. The presence of SRY is routinely tested using FISH. Phenotypic sex determination involves a cascade of genes located on the autosomes and sex chromosome, and DSDs have been associated with a number of autosomal deletions and duplications. Some of these include known DSD loci, such as SOX9, whereas others presumably harbour DSD genes that are yet to be discovered.

In recent years, traditional chromosome analysis has been replaced by molecular karyotyping, also known as chromosome microarray analysis. Molecular karyotyping allows the determination of copy number at more than a million different loci across the genome, offering detection of small chromosome deletions and duplications at a resolution that is more than 100 times greater than microscope karyotyping. Molecular karyotyping is a valuable diagnostic tool for the detection of gene copy number changes affecting known DSD genes, and is also used for research to identify new DSD loci (Ledig et al. 2010). The diagnostic yield of molecular karyotyping is greatest in DSD patients who have additional syndromal features, such as intellectual disability or associated birth defects. Despite the clear benefits of molecular karyotyping, microscope karyotyping should still be performed in DSD cases due to its ability to detect balanced translocations and low level mosaicism.

20.6.2 Gene Testing

Genetic testing for a number of DSD genes is now available on a clinical basis, including testing of SRY, androgen receptor, DHH, NR5A1 (SF-1), SOX9, WT1 and CYP21A2. This number will undoubtedly increase as new genes are identified and linked to DSDs. Detection of a specific gene mutation can assist by confirming and refining a clinical diagnosis, clarifying the risk to other family members, and providing the opportunity for molecular prenatal diagnosis in future pregnancies. Families should be aware, however, that genetic testing does not provide clear answers in all cases. In some cases a sequence variation of unknown significance may be identified. These are variations in DNA for which there is insufficient evidence to clearly classify the variant as being disease causing. In other cases, no mutation is identified, and there are several explanations for this finding. These include that a disease-causing mutation is present in a gene that was not tested, or a gene that is yet to be discovered, or that there is a mutation in the tested gene, but that it was not detected by the particular testing method used.

Currently, most genetic analysis is limited to a small number of specialized laboratories and initial mutation detection usually takes many weeks or months. It is, however, anticipated that new gene sequencing technologies (next generation DNA sequencing) will soon enable large numbers of DSD genes to be simultaneously tested at relatively low cost, providing a new and valuable tool for the diagnosis of DSDs.

20.7 Genetic Counselling for Specific DSDS

20.7.1 Sex Chromosome DSDs

20.7.1.1 47,XXY

Klinefelter syndrome (47,XXY) is caused by the presence of an additional X chromosome in an otherwise male karyotype. Sibling recurrence risk for 47,XXY is low, and probably not significantly increased compared to the background population risk, with only one documented occurrence of brothers with Klinefelter syndrome (Woods et al. 1997). There is a modest maternal age effect, resulting from approximately 30% of Klinefelter syndrome being caused by a maternal meiosis I error (Gardner and Sutherland 2004).

In the absence of medical intervention, men with Klinefelter syndrome are infertile. Instances of documented natural fertility are extremely rare (Juul et al. 2007; Laron et al. 1982; Terzoli et al. 1992) and may be accounted for by undetected XY/XXY mosaicism. In fact, testicular XY/XXY mosaicism appears to be relatively common, even in males with non-mosaic XXY on blood karyotype. Evidence from testicular biopsies of male with non-mosaic Klinefelter syndrome indicates that spermatogenesis, where present, originates not from XXY cells, but from foci of spermatogenesis with a 46,XY karyotype, most likely representing clones of spermatagonia that have randomly lost one X chromosome (Bergere et al. 2002).

Some men with Klinefelter syndrome are now able to become fathers with the assistance of testicular sperm extraction (TESE), which is able to obtain sperm in approximately 50% of XXY males (Fullerton et al. 2010). The few single sperm obtained are injected into the egg using intra-cytoplasmic sperm injection (ICSI). The first such child from a father with Klinefelter syndrome conceived using this technique was born in 1997 (Bourne et al. 1997) and since then more than 100 genetic children have been born to non-mosaic Klinefelter patients (Fullerton et al. 2010).

These successes raise the question of whether there are genetic risks to the offspring. In terms of clinical outcome, results are reassuring, with only one documented instance of foetal XXY (Ron-El et al. 2000). Nonetheless, there is some evidence that sperm from XXY males have a higher incidence of aneuploidy compared to XY males, and that this aneuploidy affects autosomes as well as sex chromosomes (Levron et al. 2000; Rives et al. 2000). These aneuploidies are most likely the result of a compromised testicular environment rather than the presence of XXY cells per se, and the risk of abnormality is similar to that for azoospermic men with a 46,XY karyotype (Levron et al. 2000; Palermo et al. 2002). On the basis of this information, there may be a small increased risk for both sex chromosome and autosome aneuploidy in the offspring of XXY males, and PGD or prenatal genetic diagnosis could be offered to these couples (Staessen et al. 2003).

For males with mosaicism XY/XXY in the blood, natural fertility may be possible, and a semen analysis in late adolescence can help predict the likelihood of natural pregnancy. In mosaic males with oligospermia or azoospermia, treatment with ICSI ± TESE may be beneficial, and XY/XXY mosaicism appears to be associated with a higher rate of sperm retrieval (Seo et al. 2004) and a lower rate of sperm aneuploidy (Ferlin et al. 2005) compared to non-mosaic XXY.

20.7.1.2 45,X

Turner syndrome (TS) is associated with partial or complete loss of one X chromosome (Nielsen and Wohlert 1991; Stochholm et al. 2006), and is characterized by ovarian failure, which occurs before puberty in most cases. While infrequent at birth, 45,X karyotype is common at conception and is identified in approximately 10% of products of conception from spontaneous abortion (Kajii et al. 1980). There is no evidence of an increased risk of sibling recurrence.

Approximately 30% of women with TS have a mosaic karyotype in the peripheral blood, with a 45,X cell line detected in conjunction with one or more other cell line, for example, 45,X/46,XX, 45,X/47,XXX and 45,X/46,XX/47,XXX accounting for variability in phenotype and ovarian function (Hanson et al. 2001).

Spontaneous puberty occurs in 15–30% of girls with TS and 2–5% experience menarche (Pasquino et al. 1997). Oocytes are present in the ovaries of approximately a quarter of adolescents with TS, but spontaneous pregnancy is rare (Tarani et al. 1998), and for many women with TS, IVF with a donor egg is the most viable option. In a Danish study based on a national TS register, none of 200 45,X women achieved a natural pregnancy (one had twins by ovum donation) (Birkebaek et al. 2002).

Current evidence suggests that 45,X germ cells are unable to complete meiosis (Modi et al. 2003), suggesting that spontaneous pregnancy in women with 45,X TS relies on the presence of 46,XX germ cells in the ovaries, with the occasionally observed follicles originating from small numbers of 46,XX germ cells (Hall et al. 2006). Fertility is more likely to be retained in women with 45,X/XX mosaicism than standard monosomy (45,X), although premature ovarian failure is common (Blair et al. 2001), and the risk of chromosomally abnormal offspring in women with mosaic TS appears to be increased compared to the general population (Sybert 2002; Uehara et al. 1999). Of note, a non-mosaic 45,X peripheral karyotype does not preclude the presence of 45,X/46,XX mosaicism in the ovary, and a peripheral blood karyotype is not a completely reliable predictor of ovarian status (Mortensen et al. 2010).

A significant proportion of women with TS have a structural abnormality of the second X chromosome, resulting in partial X monosomy. Examples are deletion Xp, ring X, and isochromosome Xq; and for these categories, mosaicism with 45,X or 46,XX cell lines is common. Many structural abnormalities of the X chromosome are compatible with spontaneous menarche and pregnancy and there are many examples of mother–daughter transmission (Lachlan et al. 2006). Risk to offspring is increased, and genetic counselling is recommended: male embryos that inherit the structurally abnormal X will usually be non-viable, and female offspring are at risk of a more severe phenotype than the mother if X-inactivation does not completely favour the intact X.

Regardless of whether conception is spontaneous or assisted in TS, increased rates of miscarriage and foetal abnormality have been described. In a review of the outcomes of 160 pregnancies in 74 women with TS, 29% resulted in miscarriage, 20% were associated with foetal anomalies such as TS and Down syndrome, and 7% resulted in perinatal foetal death (Tarani et al. 1998). Intrauterine growth restriction and prematurity occur in approximately 50% (Bodri et al. 2006). In view of the high risk of foetal anomalies, antenatal diagnostic testing should be offered to all pregnant TS women, with the pregnancy managed as high risk from a foetal perspective. Miscarriages may be due to karyotypic abnormalities such as TS or Trisomy 21, altered uterine environment related to developmental variation, or poor endometrial receptivity due to hypo-oestrogenism (Abir et al. 2001).

Pregnant women with TS require co-ordinated multidisciplinary tertiary medical and obstetric care, as they are at very high risk for complications during pregnancy, such as thyroid dysfunction, obesity, diabetes, hypertension, pre-eclampsia, deterioration of congenital heart disease, heart failure, aortic dissection and sudden death (Prac Comm Am Soc Reprod Med, 2008).

20.7.1.3 45,X/46,XY

The karyotype 45,X/46,XY is associated with a broad range of clinical phenotypes from Turner syndrome to normal male. Presumably these differences reflect the distribution of each cell line in different parts of the body, and particularly the presence of a Y-containing cell line in the gonad. Frequently, the Y chromosome is structurally abnormal, with the structural abnormality presumably predisposing to loss during mitosis.

There is substantial difference in phenotype according to whether cases are ascertained prenatally or post-natally. Prenatally diagnosed cases are phenotypic male in 90% of cases, but may be at later risk of infertility. The other 10% of prenatally ascertained cases exhibit phenotypic features of TS and/or genital abnormalities (Telvi et al. 1999). Post-natally ascertained cases present with a broad range of abnormalities, including Turner syndrome, infertility in otherwise phenotypic males and genital ambiguity. Although in theory Y chromosome instability might be familial, in practice, sporadic occurrence appears to be the rule.

20.7.1.4 46,XX/46,XY

The 46,XX/46,XY karyotype usually results from the fusion of dizygotic twin XX and XY embryos (XX/XY chimerism), although several other mechanism have been proposed. Associated phenotypes include ovo-testicular DSD, genital ambiguity, phenotypic male and phenotypic female. Occurrence is always sporadic. 46,XX/46,XY is occasionally encountered at prenatal diagnosis; in this circumstance, both cell lines may be present in the foetus, or alternatively, the second cell line result from contamination of the sample by maternal cells, or from an undiagnosed ‘vanished’ twin (Amor et al. 1999).

20.7.2 46,XY DSD

20.7.2.1 46,XY Complete Gonadal Dysgenesis (Swyer Syndrome) and 46,XY DSD

The category of 46,XY gonadal dysgenesis comprises two conditions that are phenotypically distinct but genitally overlapping.

1. 46,XY complete gonadal dysgenesis (CGD) is associated with a 46,XY karyotype, normal female external genitalia with normal Műllerian structures, and under-developed gonads with no sperm production.
2. 46,XY DSD (partial gonadal dysgenesis) is characterised by ambiguous genitalia, dysgenic tests, reduced or absent sperm production and variable presence of Műllerian structures.

46,XY gonadal dysgenesis can be familial, and is a unique example of a Mendelian disorder that can be inherited as an X-linked recessive, Y-linked, autosomal dominant or autosomal recessive trait. When inheritance is autosomal, penetrance is typically limited to individuals with an XY karyotype.

About 15% of patients have deletions or loss of function mutations in the SRY gene that are detectable by FISH or gene sequencing. The contribution of other genes is unknown; however, duplication of the gene NR0B1 (DAX1) accounts for some X-linked 46,XY gonadal dysgenesis (Barbaro et al. 2007), homozygous (or compound heterozygous) mutations in DHH account from some autosomal recessive 46,XY gonadal dysgenesis (Canto et al. 2004) and autosomal dominant 46,XY gonadal dysgenesis can result from heterozygous mutations in DHH, NR5A1 (SF1) (Philibert et al. 2010) and MAP3K1 (Pearlman et al. 2010).

A limited amount of genetic testing is available and can be used to inform genetic counselling in familial and sporadic cases of non-syndromic 46,XY gonadal dysgenesis. Analysis of SRY and chromosome microarray analysis are the first line genetic investigations, followed by genetic analysis of NR5A1, DHH, MAP3K1 and NR0B1 (duplication).

In familial cases of 46,XY gonadal dysgenesis and cases where a causative gene mutation is identified, this information will inform genetic counselling. The identification of a gene mutation allows carrier testing of family members, and prenatal diagnosis in at-risk pregnancies.

Men with SRY mutations are usually infertile, therefore most mutations arise de novo in the proband rather than being present in the father. Nonetheless, siblings of the proband might still be at low risk because of gonadal or somatic mosaicism in the father. Mutations in SRY that result in partial loss of function can cause 46,XY DSD, and penetrance may be incomplete, complicating genetic counselling.

In cases where there is no family history and no identified genetic abnormality the situation is less straightforward. No empiric sibling recurrence risk data exist, but risk is likely to be low. In the absence of molecular confirmation, prenatal diagnosis can potentially be offered by looking for the combination of an XY karyotype on CVS/amniocentesis and female external genitalia on ultrasound.

Some individuals with 46,XY DSD may be able to reproduce with the aid of assisted reproduction technologies. For 46,XY women, fertility is possible with ovum donation if a uterus is present (Michala et al. 2008). Individuals with 46,XY DSD may be able to reproduce using their own gametes and assisted reproduction technology. For mutations affecting the SRY gene, the mutations will be passed to all sons but not to daughters of the proband.

20.7.2.2 XY Ovarian Disorder of Sex Development

The development of normal female anatomy and ovarian tissue (usually dysgenetic) in the presence of a 46,XY karyotype is very rare. There is a single case report of this presentation as an autosomal recessive entity, caused by compound heterozygous mutations in the gene CBX2 (Biason-Lauber et al. 2009).

20.7.2.3 Complete or Partial Androgen Insensitivity Syndrome (CAIS or PAIS)

Androgen insensitivity syndrome is inherited as an X-linked recessive trait, and is caused by mutations in the androgen receptor (AR) at Xq11–12. The androgen receptor is the only gene known to be associated with CAIS, and sequencing of the AR gene detects mutations in >95% of patients with CAIS. PAIS appears to be genetically heterogeneous and mutations in the AR gene are found in <50% of patients (Gottlieb et al. 2007). More than 300 different AR mutations have been shown to cause AIS (http://androgendb.mcgill.ca/). The phenotype of CAIS is relatively consistent within families; however, the phenotypes of PAIS show intra-familial variability (Deeb et al. 2005). De novo mutations are relatively common, being observed in 27% of families with only one affected individual (Hiort et al. 1998). Therefore, genetic testing is necessary to provide accurate genetic counselling. Gonadal mosaicism has also been reported for AIS (Boehmer et al. 1997). Therefore, there is a small risk of recurrence even following an apparently *de novo* mutation.

When a female is known to be heterozygous for an AR mutation, for each offspring, there is a 1 in 4 chance of the offspring having a 46,XY karyotype and being affected by AIS, and a 1 in 4 chance of the offspring having a 46,XX karyotype and being a carrier of AIS. Prenatal diagnosis and pre-implantation genetic diagnosis (PGD) are available for AIS.

Note that AIS is allelic to Kennedy disease (Spinobulbar muscular atrophy), which is caused by the expansion of a polyglutamine tract within the AR gene. Patients with Kennedy disease have mild AIS.

20.7.2.4 Hormone Biosynthetic Defects

Defects in androgen biosynthesis can lead to normal testis development but incomplete androgenisation of male genitalia. Some disorders are accompanied by deficiencies of adrenal hormones. Examples are 17β-hydroxysteroid dehydrogenase deficiency, 3-beta-hydroxysteroid dehydrogenase deficiency, cholesterol desmolase deficiency and 17α-hydroxylase deficiency. Inheritance is autosomal recessive, therefore there is a 1 in 4 risk of recurrence in each pregnancy; however the genital phenotype is only expressed in individuals with a 46,XY karyotype.

Smith-Lemli-Opitz syndrome (SLOS) is a rare autosomal recessive multiple congenital abnormality syndrome caused by deficiency of the enzyme 7-dehydrocholesterol. In XY individuals, there is incomplete androgenisation of the male genitalia.

20.7.3 Rare Syndromes

20.7.3.1 Campomelic Dysplasia and SOX9

Campomelic dysplasia is a rare skeletal dysplasia characterised by long bone bowing (campomelia), cleft palate, club feet and distinctive facies. In XX individuals, normal female genital development occurs; however most XY Campomelic dysplasia patients have either female or ambiguous external genitalia and variable internal genitalia. SOX9 is the only gene associated with campomelic dysplasia, and inheritance is autosomal dominant, although most cases result from *de novo* mutations. About 5% of affected individuals have a chromosome translocation, visible in standard karyotype, disrupting the SOX9 locus at 17q24.3–25.1. Translocations are usually *de novo*, but parental karyotypes should nonetheless be checked, as translocations with breakpoints at a long distance from SOX9 may have incomplete penetrance. The remaining 95% of patients have a sequence change, or less commonly a large deletion, affecting SOX9. Germ line (Cameron et al. 1996) and somatic (Smyk et al. 2007) mosaicism for SOX9 mutations has been reported. Of note, some individuals with SOX9 mutations and ambiguous genitalia have normal skeletal development.

20.7.3.2 WT-1

Denys-Drash syndrome and Frasier syndromes are both caused by autosomal dominant mutations in the gene WT-1 located at 11p13, with the majority of mutations being *de novo*. Denys–Drash syndrome is characterised by early-onset nephropathy, increased risk of Wilms' tumor and 46,XY DSD. In Frasier syndrome, nephropathy is later in onset, there is 46,XY complete gonadal dysgenesis and tumour risk is primarily for gonadoblastoma. For both conditions, XX individuals usually have normal genital development.

20.7.4 Isolated Abnormalities

20.7.4.1 Hypospadias

Hypospadias is a common abnormality where the urethra opens on the ventral side of the penis, and is associated with a range of Mendelian syndromes, chromosome abnormalities and DSDs. For isolated hypospadias, the risk of recurrence in male siblings is around 1 in 20, and a similar risk applies for sons of an affected male. X-linked hypospadias has been reported in association with mutations in the gene MAMLD1 (Fukami et al. 2006) and with mutations in the androgen receptor (Allera et al. 1995).

20.7.4.2 Cryptorchidism

Cryptorchidism is a common abnormality in males, and is thought to result from a combination of genetic and environmental factors. The recurrence risk in male siblings of isolated cases is around 1 in 20 (Czeizel et al. 1981). Cryptorchidism is also associated with a range of Mendelian syndromes and chromosome abnormalities.

20.7.5 46,XX DSD

20.7.5.1 XX Testicular Disorder of Sex Development

Most males with XX Testicular DSD arise as a result of the presence of SRY in an otherwise normal XX karyotype. The phenotype is similar to that of Klinefelter syndrome, with male external genitalia, small testes, azoospermia and, if untreated, signs of testosterone deficiency. In contrast to Klinefelter syndrome, males with XX testicular DSD do not have increased stature or learning difficulties (Ferguson-Smith et al. 1990). In most males with SRY + XX testicular DSD, Yp material (including SRY) is present on the X chromosome as a result of abnormal exchange during meiosis I during gametogenesis in the father. This is nearly always a sporadic event (Wang et al. 1995; Weil et al. 1994). Far less commonly, SRY has been translocated onto a terminal arm of an autosome (Dauwerse et al. 2006; Queralt et al. 2008), and in this circumstance, sex-limited autosomal dominant inheritance is observed. There is also on record a normally fertile XY individual in whom SRY was translocated onto the X chromosome (Abbas et al. 1993); in this circumstance, all XX offspring would have XX testicular DSD. Because of these rare familial occurrences, in order to prove sporadic occurrence, it is necessary to perform FISH to search for SRY in the father and confirm that SRY is located only on the Y chromosome. Men with SRY + XX testicular DSD are infertile.

A minority of males with XX Testicular DSD are SRY negative, and the DSD presumably arises from inappropriate activity of the gene cascade that is normally switched on only in response to SRY. Not surprisingly, genital ambiguity occurs more commonly in these patients. The cause of testicular development in these patients is not well understood but abnormal dosage of genes in the sex-determining pathway is likely to play a part. One family has been reported with autosomal dominant sex-limited transmission of SRY-testicular DSD, resulting from a 178 kb duplication 600 kb upstream of SOX9 (Cox et al. 2011). In the absence of family history, risk of recurrence is likely to be low. XX testicular DSD has been diagnosed prenatally, following the detection of discordance between chromosomal and ultrasonographic sex (Trujillo-Tiebas et al. 2006).

20.7.5.2 46,XX Ovo-Testicular DSD

Individuals with 46,XX, ovo-testicular DSD have both testicular and ovarian tissue (containing spermatogonia or oocytes, respectively, either within the one gonad or in separate gonads). The karyotype on peripheral blood is 46,XX and SRY is absent. The likely explanation is localised activation of testicular development, for example, by cryptic mosaicism within the gonad for cells containing the SRY gene (Ortenberg et al. 2002; Queipo et al. 2002) or other mosaic mutations that lead to testicular development. Most cases are sporadic, but the existence of rare familial cases (Ramos et al. 1996; Slaney et al. 1998) indicates the existence of yet-to-be identified X-linked or autosomal predisposition genes.

20.7.5.3 Congenital Adrenal Hyperplasia (CAH)

CAH is a family of disorders characterised by impaired synthesis of cortisol from cholesterol in the adrenal cortex. At least eight forms exist and all follow autosomal recessive inheritance. The most important type is 21-hydroxylase deficiency, which causes virilisation in XX individuals and variable salt wasting in XX and XY individuals. Molecular testing of the gene *CYP21A2* detects mutations in most cases and can be used for prenatal diagnosis. Genital ambiguity in female foetuses can be reduced or eliminated by suppressing foetal androgen production by the administration of dexamethasone to the mother from early pregnancy until delivery (Nimkarn and New 2006). Dexamethasone needs to be commenced in all pregnancies, but can be ceased in seven out of eight pregnancies when prenatal diagnosis shows either that the foetus is male, or is female but unaffected by CAH. For affected females who are adequately treated, pregnancy is possible, although fertility rates are reduced (Lo et al. 1999).

20.7.5.4 Rare Syndromes

Several rare syndromes exist in which male genital development occurs in the setting of an XX karyotype and other abnormalities.

Mutations in the R-Spondin1 gene cause a syndrome of *XX testicular DSD, palmoplantar keratosis and squamous cell carcinoma of the skin* (Parma et al. 2006). Inheritance is autosomal recessive, and in XY individuals only Palmoplantar Keratosis (PPK) and Squamous Cell Carcinoma (SSC) are present.

Microphthalmia with linear skin defects syndrome (*MLS*) is an X-linked male-lethal disorder associated with X-chromosome rearrangements that result in monosomy from Xpter to Xp22, including the gene HCCS. In some individuals, the chromosome rearrangement is an X;Y translocation, resulting in sex reversal due to translocation of SRY onto the X chromosome (Mucke et al. 1995).

46,XX sex reversal in association with multiple congenital abnormalities has also been reported in a patient with a chromosome 22 duplication, 46,XX,dup(22)(q11.2q13). The patient had male external genitalia and intra-scrotal gonads (Seeherunvong et al. 2004).

20.7.5.5 Isolated Abnormalities

Műllerian abnormalities including uterine and vaginal agenesis, and duplication of the uterus and vagina, are relatively common, and undoubtedly under-diagnosed. Ovarian function is usually normal, and presentation is commonly at puberty with menstrual abnormalities, or later with infertility or pregnancy complications. Although genetic factors are likely to contribute, most isolated Műllerian abnormalities are sporadic and risk of recurrence is low. There is a known association with renal and skeletal abnormalities, which in its most severe form is known as MURCS association (Műllerian duct aplasia, unilateral renal aplasia and cervico-thoracic somite dysplasia) (Duncan et al. 1979). MURCS association is usually sporadic, but familial forms exist and autosomal dominant inheritance with incomplete penetrance has been suggested (Guerrier et al. 2006). Abnormalities of female internal and external genitalia are also associated with a large number of rare genetic syndromes and a variety of chromosome abnormalities.

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Cultural Differences and Controversies About Timing of Management

21

Garry L. Warne and Vijaylakshmi Bhatia

21.1 Introduction

The management of infants and children with DSD varies from country to country, and between Asia and western societies, there are many differences in the approach taken. The differences arise partly from the level of poverty in Asia. Poor parents cannot easily access high-quality medical services. The differences also stem from the culture. The collective beliefs and attitudes that make up the cultural background inevitably influence the way in which all people, both lay and professional, think about medical management issues. It may be difficult for any of us to discern the cultural influence on our decision-making from 'inside' the culture and stepping 'outside' may give a glimpse of one's own culture as others see it.

In the west, the medical profession and DSD patient-advocacy groups have engaged, over the past decade, in a vigorous and healthy exchange of views about ethics. The main issues relate to the nature and timing of genital surgery and the disclosure of medical information to parents and patients. On the latter subject, there is now widespread agreement that full disclosure is essential and the only questions remaining are 'when and how'? Whether genital surgery should be done when the patient is still an infant or a young child is still highly controversial because, it is argued, the consent of the person affected cannot be obtained. The alternative suggested is to postpone surgery until the individual is old enough to have a say. Most paediatricians and paediatric surgeons think that early surgery is best and most patient advocates oppose it. A very vigorous discussion is taking place and a better understanding of the different positions is emerging, with some willingness on each side to compromise.

In many Asian countries, however, especially in the poorer ones, children with ambiguous genitalia grow up with the anatomy they were born with and if they have surgery at all, it may be left until they are in late childhood or even adolescence. The culture accepts this when people see no alternative. Every Asian village has children and adults with deformities and disabilities. People are used to seeing them. How, then, do children with ambiguous genitalia fare under these conditions? Are they treated with respect and dignity, allowing them to grow up with intact self-esteem and empowered to make their own decision about when to undergo surgery, or whether they need to have surgery at all?

In this chapter, we attempt to take a trans-cultural look at the outcome for DSD patients, based on experience the authors have had working in India, Vietnam and Australia.

DSD, which are many and varied, are the postnatal manifestations of significant variations in foetal reproductive tract development. Most stem from aberrant chromosomes or single-gene mutations, often associated with secondary hormonal disturbances in various combinations that continue to exert their effects on the affected individual throughout life unless treated

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appropriately. The possibilities include sex hormone deficiency, androgen excess, cortisol deficiency and mineralo-corticoid deficiency or excess. The external anatomy of the urogenital tracts is what draws attention to the presence of the condition, but affected people also usually have to deal with issues related to sexuality, infertility, emotional health and how they relate to others in the community in which they live. The social dimension often becomes as important as the medical dimension. We are all the product of our environment and this is no less true for the person with a DSD than for the rest of us.

In this chapter, we examine treatment outcomes for people with DSD in three countries: India, Vietnam and Australia. Our aim is to show how the cultural setting influences doctors and parents when they make decisions about children with DSD.

Men and women have different roles in all human societies, eastern and western. Unless compelled to do otherwise, as in Chairman Mao's China, men dress differently from women. They use language differently, behave differently and follow somewhat different interests. According to Freud and Foucault, all adult human relationships have a sexual component and this is recognized by all of the major religions. From a very early age, children recognize their genitals as their own and make the association between genital appearance and gender identity. People want to be clearly identifiable as male or clearly female because sex is a fundamental part of personal identity and uncertainty about sex disturbs other aspects of identity. Trans-sexual individuals identify strongly with one gender, albeit one that is discordant with their birth sex, and cannot understand why other people cannot see them as they see themselves.

The laws of both civil and religious societies differentiate between males and females. Except in those few places that have recently begun sanctioning same-sex marriages, legal marriage requires a man to marry a woman. The definition of 'man' and 'woman' comes down to a decision made at the time of the person's birth, based on a cursory inspection of the external genitals by someone who might well have no professional training. Once the birth sex is registered, it is difficult to change unless it can be shown that an error was made. Laws of inheritance are often gender-specific. In Islamic law, ownership of property may only pass from father to son. Other societies, such as that of Mangalore in South India, are matriarchal and in these, property may only be passed down from mother to daughter. Certain religious occupations, such as the Roman Catholic priesthood and clerical roles in Islam, are restricted to men. In traditional Judaism and Islam, places of worship are segregated, with separate places for men and women (with the men being more central to the worship than the women).

In India and Vietnam (and in many other places where there are insufficient public toilets) men commonly urinate in public places without causing offence, but women are required to hide themselves from view for the same function. In many traditional societies, women segregate themselves from their families during menstruation (and may temporarily go to live in a separate dwelling) because they are regarded as ritually unclean.

Indian society places great importance on marriage. For a woman, it is the key to any existence separate from her parents because her husband will then support her. If she does not marry, if she is widowed, or worse still, if she is divorced, she may well become unemployable and reduced to wretched poverty because of the stigma attached to being single. An unmarried man, on the other hand, can find employment and survive independently. Marriages are mostly arranged and are considered to be for the purpose of producing children. If the parents know that their son or daughter will never be able to have children, for example because of irreversible gonadal failure, they cannot offer that child to be married. If the child is female, she will remain unemployed and be the responsibility of the parents forever. If they fail to disclose their knowledge of the child's infertility (regardless of gender) to the other family and allow the marriage to go ahead, the marriage can immediately be annulled once the situation is revealed. Health professionals who may be planning to disclose sensitive medical information to parents need to be very mindful of this. The father of one girl with complete AIS told the authors that he wished they had never told him that his daughter would be unable to bear children. If things had been left uncertain, he could have offered his daughter in marriage.

Once married, men are subject to values that are different from those applied to women. Unfaithful husbands are tolerated (many men in India and Vietnam have extramarital relationships), but wives are expected to be unwavering in fidelity and are severely punished if they stray.

Societies differ markedly in their tolerance of various forms of sexual behaviour. In India and Vietnam, people commonly assert to western enquirers that homosexuality is rare in their communities. Homosexuals in India wisely keep a low profile (or opt out of general society and join a fringe group known as *Hijra*, or 'hermaphrodites' society') (Nanda 1996; Kucheria et al. 1988) because homosexuality arouses intense disapproval in the minds of the population. Western societies, on the other hand, have decriminalised homosexual acts between consenting adults in private, acknowledge that it is common and increasingly accept it as a normal variation. Many major cities, such as Sydney, London, Toronto, San Francisco and Copenhagen hold Gay and Lesbian Festivals. In the Highlands of Papua-New Guinea, all adolescent males are encouraged to engage in oral sex with other boys because of religious beliefs that the ingestion of semen is essential for the development of masculinity (Herdt 1996). In Samoa, it is very common for boys perceived as having more feminine characteristics to be raised as girls who are then expected to help the mother as if she were a daughter. These boys who live as girls are called *fa'afafine* (Besnier 1996). Although fa'afafine are not always effeminate or homosexual, they will live, dress and behave like females. They are respected, hardworking members of society.

People with DSD are likely to have been the subject of medical and parental confusion concerning their sex when they were born or when the condition was first diagnosed. During childhood and adolescence, they may experience confusion about who they are and what sex they are. How do they then fit into their society and how does society regard people whose sex is in any way unclear? This chapter focuses on how societies differ around the world in their views about sex and sexual differences and will present evidence from clinical research on the long-term outcome for young people with DSD in three countries, namely India, Vietnam and Australia.

In each of these three cultural settings, let us assume that the parents and the health professionals whom they consulted were seeking the best possible outcome for the child. But all of the decision-makers (parents and health professionals alike) were also products of their environment. Their decisions reflected not only the medical facts of the case, but also the cultural setting and belief system in which the problem was being considered. By comparing the outcome for children with DSD living in cultures as different as that of Lucknow, in northern India, Hanoi in northern Vietnam and Melbourne in southern Australia, we have the opportunity to discern some of the cultural influences on medical decision-making. We can also look at differences arising from the timing of genital surgery, because in India and Vietnam, surgery to make the genitalia look male or female is commonly performed in late childhood, adolescence or even adult life, whereas in Australia, the same surgery is usually carried out when the baby is 4–6 weeks old.

21.2 Thoughts of a North Indian Paediatric Endocrinologist

Dr Vijayalakshmi Bhatia: The ethical considerations in the management of DSD in India and similar other cultures, as distinct from Western cultures, are, to an extent, highlighted by the evolution of my own philosophy of management of patients with these disorders as I graduated from a paediatric endocrinology fellowship in the USA to return to my own country to work as a faculty member in a teaching hospital.

When I was a trainee in the late 1980s, the guiding principle for decisions regarding sex of rearing, in almost all patients except virilising CAH, was, in a nutshell, the size and development of the phallus. If the phallus length and amount of corporal tissue palpable were generous, a male sex of rearing was advised. If this was not the case, a female sex of rearing was advised, based on the premise that a neo-vagina with prospect for satisfactory sexual function could be easily surgically fashioned, whereas the possibility of creating the functional male phallus from a poorly formed pre-existing structure was low. Probably, since that time, Western thinking has also changed. With the realisation that patients with conditions like 5-α reductase-2 deficiency and 17-β-HSD deficiency are more likely to develop a male gender identity, as well as the fact that a somewhat smaller adult phallic length is still compatible with satisfactory sexual function, many more under-virilised male babies are being reared as male rather than female.

However, we hark back to 1989 when I returned to my country, fresh with the ideas imbibed during my training. I returned to a challenging new set of conditions in the most populous and backward state of my country. Some were the outcome of late presentation and treatment, due to economic hardship and scant medical facilities, while others were a reflection of different social mores. I encountered genotypic females with CAH presenting untreated for the first time to a well-equipped centre at the age of 5–10 years and beyond, fully virilised and often brought up mistakenly as boys. For these children who were unambiguously reared male, and were already old enough to have a firmly set gender identity, I felt my duty lay in explaining everything to the parents, in encouraging continuation of the male sex of rearing, and performing necessary supportive surgery and giving hormonal therapy. Such psychological and social support as could be provided by myself and colleagues in the department was the only source of support for these families, there being no social worker or psychologist trained to provide counselling for these disorders in or near my city.

With families of genotypic females with virilising CAH who were brought to our attention during infancy, I often experienced frustration. Contrary to expectation, parents often did not accept a female sex of rearing despite the assured possibilities of menstruation and reproductive capability. I attribute it to ignorance and fear of raising a female child with any hint of a reproductive disorder. Unfortunately, many of these families would discontinue follow-up altogether, despite my assurances that regarding sex of rearing, theirs was the final decision, and it would be respected. This experience was different from that published from south India. Reporting on 23 genotypic females with CAH, (Jini et al. 1993) stated that all parents accepted a female sex of rearing (including parents of five patients who had been brought up as boys prior to the clinic visit) because fertility was possible. In contrast, most parents of 30 undervirilised genotypic male patients preferred a male sex of rearing for their child if, in the future, the child would not be able to reproduce as a woman. It is possible that the advanced literacy rate and progressive society encountered in south and central India allowed for appreciation of the better expected outcome of CAH in contrast to other types of DSD.

The group which brought out the starkest contrast between East and West were under-virilised genotypic males. These babies almost always had a male sex of rearing when brought to us, the visible or palpable external gonad/gonads having given a clue to the parents about the sex of the baby. After explaining the possible disease to the parents, I would emphasize that if brought up as a male, the future man may not be able to have satisfactory sexual function, whereas the chances were high of satisfactory sexual function with a feminising genitoplasty. Back came the reply, invariably: ‘If she cannot bear children, or worse still, cannot even menstruate, there is no chance of her getting married. Any talk of sexual function is irrelevant’. I would persist: ‘Don’t think of only discharging your responsibility. Put yourself in the shoes of your son 20 years hence when he is about to be married, and think whether he will be happy’. The coherent reply: ‘Doctor, at least he will be able to survive. He will have a job. God willing, and if the boy wants it, he will marry, else he won’t. As a girl, she will be all alone in this world with no one to care for her after we, her parents, are no more’. Me, in my misguided zeal: ‘You must also consider the possibility that you can educate your daughter to be as economically independent as your son. She may even choose her own partner. Then there will be no compromise’. Parents: ‘Doctor, we have to raise her in our society, not yours’.

My society and theirs: In India, the land of disparities, my society is represented by a fortunate few; highly educated though still quite traditional compared to the West. The status of women is improving though far from equal to men. Though not commonly encountered, it is possible for a single woman to be a happy productive member of my society. But ‘their’ society, which represents more than 75% of India is highly traditional, with a woman having no rights and no status except through her father or husband. Even if a girl has graduated from college and is employed, a father is not seen to have discharged his duties as a parent if he does not marry off his daughter. Marriage is arranged and partners are selected by the parents or other elders. Thus, a parent is likely to encounter difficulties finding a groom for his daughter who cannot bear children. Many girls with such disorders would be married to a widower with children or be forced to compromise in some other (financial or social) way. In such a male-dominated society, no one questions the justice of a male with serious doubts on his ability for conjugal relations or to procreate, getting married without first informing the bride and her family! On the other hand, if the same is done for a girl, and the truth is found out later, she is sent back in disgrace to her father’s house or faces other more serious consequences in the house of her in-laws.

Of course, we seem to be coming full circle as far as under-virilised male disorders are concerned. Happily for us, the scientific evidence which is emerging suggests that male sex of rearing is not only a possibility but to be preferred in many of these patients, giving me reason to conclude that social necessities are not always at variance with science in this group at least.

As I continued to work with and learn from my patients, I found an equally absorbing and sometimes acrimonious debate evolving in the Western world. I was aware that there had always been differences of opinion among the giants in the field of DSD, as to the timing and nature of genital surgery. Investigators were constantly looking for evidence upon which to base their practice. Due to inadequate numbers of long-term outcome studies, the guidelines for surgery could not yet be carved in stone. Physicians and surgeons therefore did what they considered best for their patients, until more data emerged. Now, patient advocacy groups were trying to force the pace of change in management practices. As regards timing of genital surgery in India, the considerations in the minds of our patients may (or may not) be quite different from those in Western cultures. I allude to this issue further in this chapter. But it was the issue of disclosure, also hotly debated at this time, which made me compare the situation in India with that in developed countries.

In fact the situation was the exact reverse in India, with parents knowing early on the nature of the disorder in their baby and playing the primary role in choosing the sex of rearing for their child. This was necessitated by the extant social and economic circumstances in my country. Due to the factors mentioned above, decisions about sex of rearing were dictated as much by social considerations as by medical ones. Obviously, the social considerations relevant to the child can be best interpreted by the parents rather than the doctor. Therefore, it was necessary for the specialists caring for the child to place all the facts before the parents so as to enable them to make as informed a decision as possible. Secondly, due to the poor state of medical records in our institutions, the poor facilities for communication and the overwhelmingly large area of our country, it was simply not possible to ensure that information about a patient could be made available to another institution or doctor when the need arose. Therefore the patient's family had to be the vehicle for transfer or safe-keeping of all records.

In contrast to all this, in advanced countries, the first consultation with specialists for DSD occurs early in the newborn period, when parents have had no time to get over their grief of their baby being born with a serious disease. Since medical considerations rather than social ones were to be the guiding principles, the doctors may use language which will 'soften' the shock to the parents rather than to speak the blunt language of scientific jargon. The following example is a case in point. I heard a paediatric endocrinologist in an advanced country counselling the parents of a newborn baby with complete androgen insensitivity syndrome (CAIS) thus: 'Your baby was never meant to be a boy'. Obviously, this was an interpretation of the effect complete lack of androgen receptors has on the body. In my country, no matter how convinced I was of the advisability of rearing a child with complete AIS as a girl (even in the circumstances of my country), I would still have to counsel the parents thus: 'Your baby would have been a boy if nature had had its way and no disease had interfered. However, the nature of the disease is such that the child cannot function and may not even look externally or sound like a male. However, if you decide to bring up the baby as a daughter, the following are the advantages….' I know parents of babies with complete AIS who have still decided to bring up their babies as boys.

People in other countries are intrigued by the Hijra group in India and want to know what connection, if any, they have with DSD. They are mainly comprised of people with a gender-identity disorder or else boys who have been kidnapped and castrated and forced to join the group. Though they wear women's clothes and have female names, they don't look and sound very feminine. Contrary to popularly held belief, they are not patients with DSD. They live in separate, close-knit groups and do not like to reveal the details of their life to 'outsiders' (Ammini AC, personal communication). Their well-known way of making a living in north India is by singing and dancing at births and weddings (uninvited, of course, but they will not budge until paid handsomely). They also indulge in prostitution. In general, their group is viewed with fear and suspicion and often subjected to ridicule.

Does their presence have any bearing on families with a baby who has a true DSD? Yes and No. Very few parents have ever asked me whether their baby is hijra. Perhaps, the very idea and word are too repugnant to them to associate with their child. Most word their question thus: 'Will my baby grow up to be clearly one sex, after we do the necessary treatment?' As to the few parents who have mentioned it, I have had no difficulty explaining to them that their baby is very different from the hijras. However, they do have an underlying fear that if a hijra group discovers that their baby has genital ambiguity, they will forcibly take the baby away. Obviously, this fear is greater among the lowest socio-economic rung of our patients. All said and done, my colleagues and I always bear in mind that the words we use during counselling should alleviate the spoken or unspoken fear in the parents' mind of their baby being hijra.

21.3 Observations on 29 DSD Patients in Hanoi, Vietnam

Professor Garry Warne: The Socialist Republic of Vietnam is a communist state with a predominantly rural population of 83 million and an average life expectancy at birth of 70.3 years. The literacy rate is 90.3% but the country is poor, with GDP-per capita of $2,500. The religions are Buddhist, Hoa Hao, Cao Dai, Christian (predominantly Roman Catholic, some Protestant), indigenous beliefs and Muslim. The capital city, Hanoi, has a population of approximately 3 million and a surrounding population of perhaps 30–40 million.

Medical care is provided through commune health stations, district, provincial and central hospitals and is on a fee-for-service basis except for children under the age of 6 years. The percentage of GDP spent on health is 1.29% and the per capita funding for health is $US28 per annum. All medicines must be paid for. For many people, comprehensive Western-style health care is unaffordable and they prefer to try cheaper traditional medicines and therapies in the first instance. A chronic illness in any member of a poor family is very threatening for economic reasons. The cost of even simple medications, such as oestrogen tablets, may place enormous strain on the budget of a Vietnamese family. Hospital stays for children are usually longer than in the west (average length of stay 8–10 days) because after-care in the community is lacking. The parents are required to stay with the child in hospital and provide food, which means that they cannot work and have no income for that period.

The only paediatric endocrinology department in Vietnam is at the National Hospital of Paediatrics in Hanoi. This is a 500-bed hospital built with Swedish assistance after the end of the Vietnam War and opened in 1980. The range of laboratory tests available to it is very limited and it is not possible to fully investigate DSD. Most patients come from the northern provinces surrounding Hanoi but some come from very distant provinces in the central part and south of the country. Mental health issues receive little attention. Although the hospital has a Department of Psychiatry, it is overloaded and cannot provide a counselling service. There are also no genetic counsellors or social workers.

21.3.1 The Study Sample

The Head of the Endocrinology Department at the National Hospital of Pediatrics, Professor Nguyen Thu Nhan, invited 29 families to attend for interview. Patients were included if they had a DSD, were available and either they or their parents were willing to speak to the interviewer. Some were included because the child was a current in-patient, and others attended expressly to have the child reviewed by the visiting expert. The average age of the patients when they first saw a doctor was 3.2 years and at the time they were seen for this study, 8.9 years, with 6 aged 12–27 years. Very few parents spoke English at all and one of the endocrinologists, Dr Bui Phuong Thao, interpreted for all interviews. Interviews were unstructured but mainly focused on the experiences of the parents when their child was born and as they sought medical assistance. Their feelings were explored and for many parents, it was the first time anyone had asked about their emotions. Most parents were asked an open-ended question without reference to gender about their child's behaviour, but in answering most parents related the behaviour to the assigned gender. They were invited to say what concerned them about the child's future. Older patients were interviewed without their parents if all consented.

Details for all 29 patients and a summary of the author's contemporaneous notes are recorded in the Table 21.1.

There was initial indecision and confusion when the child was first recognized to have a DSD. Referral to a specialist was often delayed (patients 1, 3, 5, 6, 8, 9, 10, 11, 12, 16, 20, 24, 26) and health workers who had no background knowledge of the conditions often gave parents reassurance that was totally inappropriate.

The child and often the parents were stigmatized in the village because of the sexual ambiguity (patients 1, 5, 10, 12, 20, 24). A particularly pejorative Vietnamese

Table 21.1 Details on 29 patients seen in Hanoi, Vietnam

Patient ID	Age when seen	Age at presentation	Genitalia at birth	Assigned sex	Gender behaviour	Medical condition	Had genital surgery?	Clinical details and comments
1	4	Birth	ambig	M	M	46XX/46XY gonadal dysgenesis	N	Microphallus, perineal orifice, R. gonad (2 mL) palp, L gonad not palp. No mullerian structures. Initially advised to defer investigation and surgery. Risks of surgery & infertility not disclosed to parents yet. Significant social difficulties for child and parents in village already.
2	1.25	Birth	Ambig	M	?	PAIS	N	Phallus 1 cm, perineal orifice, 2 testes, labia-like genital folds. No karyotype. LH 3, FSH 3.8. testosterone 20.6 nmol/L. Ultrasound not done. Surgeon wants to wait until age 3 before operating.
3	7	Birth	Ambig	F	M	No investigations	N	Phallus 2.5 cm, separate genital folds, only L gonad palpable, looks and acts like boy. Probable partial GD. Seen by doctor at birth, parents advised not to worry. When child (girl) started school, teacher urged consultation. Parents then decided to change to a boy's name and are keen to resolve gender question quickly. Other villagers completely supportive.
4	17	Not clear	Ambig	M	F	CAH (SW)	Y (3)	46XX, elevated 17KS, low sodium, high potassium. Short stature, hyperpigmented, voice not deep. Takes hydrocortisone. Repeatedly ill in 1st 2 yrs, not since. Poor surgical result (clitoris removed). Intellectually disabled. Typical female interests but sometimes aggressive. 2 siblings died, probably from CAH (another died of a brain disease). Parents members of CAH Club.
5	0.25	6 wk	Ambig	F	?	CAH (SW)	N	Born with only mild clitoromegaly. Wait and see policy advised. Persistent vomiting started at 10d, doctor not consulted until age 6wk. Then severely salt-depleted and CAH was diagnosed. Came to a hospital 1000 km from home to avoid other villagers finding out.
6	6	2 wk	Ambig	F	F	CAH (SW)	Y (2)	Doctor diagnosed CAH immediately after birth but gave no information or referral. Subsequent vomiting led to dehydration. Seen at 2 weeks and treated with iv fluid and steroids. 46XX. Many adrenal crises before age 3y, none since. Normal linear growth. Still has urogenital sinus. Clitoris is small. Mother belongs to CAH Club.

(continued)

Table 21.1 (continued)

Patient ID	Age when seen	Age at presentation	Genitalia at birth	Assigned sex	Gender behaviour	Medical condition	Had genital surgery?	Clinical details and comments
7	6	Birth	Ambig	F	F	CAH (NSW)	Y (2)	Non-salt loser, diagnosed as neonate. Typical female behaviour. Parents concerned about future sexuality. Members of CAH Club.
8	Infant	4 wk	Ambig	M	?	CAH (SW)	N	Initially named as a male. Started vomiting at 2 weeks, village doctor reassured parents. After 2 more weeks, baby was weak and dehydrated. At hospital sodium was 97 mmol/L, potassium “off-scale”. Initial karyotype reported 46XY, later repeated and found to be 46XX. Progesterone 56 nmol/L, testosterone 84 nmol/L. Now on hydrocortisone (Cushingoid). Long clitoris and perineal urogenital sinus.
9	27	20	Ambig	F	M	CAH (NSW)	N	46XX, identified as girl until age 14 then independently started transition to male social gender. Never developed breasts or had menses, but knows ultrasound showed uterus. Progesterone 21 nmol/L, testosterone 65 nmom/L. Intelligent and successful in a responsible job. Feels unambiguously male. Attracted to females but no relationships. School friends (including girls) very supportive. Height 137 cm, phallus 5–6 cm, urogenital sinus, hyper-pigmented skin, no palpable gonads. Shaves 2–3 times/wk. Wants surgery to make genitalia male.
10	9	7 mo	Ambig	F	M	46XY, incomplete diagnosis	N	Phallus 4.5 cm, 2 palpable testes, 2 perineal orifices. FSH, LH, testosterone all low. No mullerian structures. Seen by doctor early but advised to do nothing. Still regarded as ambiguous and no decision about gender has been taken. Child wants to be a boy. Cruel and on-going verbal abuse for parents and child in village.
11	4	Birth	ambig	M	M	46XY, incomplete diagnosis	N	Saw doctor early but advised to wait 2–3 years. Typically male behaviour. Phallus 3.5 cm, peno-scrotal orifice, 2 testes in scrotum. Looks like simple hypospadias but LH, oestradiol and 17KS levels reported to be high.
12	7	6	Ambig	M	?	46XY gonadal dysgenesis	N	At his birth, parents were told he was a hermaphrodite. Grandfather (a doctor) recommended no action, so presentation was delayed 6 years. Parents’ relationship suffered and father lives in another town. Child is identified in the village as a hermaphrodite. Has a <2cm phallus with a single peno-scrotal orifice and 2 testes. FSH and LH levels elevated, testosterone undetectable, no mullerian structures.

Table 21.1 (continued)

Patient ID	Age when seen	Age at presentation	Genitalia at birth	Assigned sex	Gender behaviour	Medical condition	Had genital surgery?	Clinical details and comments
13	5	2 mo	ambig	F	M/F	CAH	Y	Diagnosed at 2 months, now on hydrocortisone and fludrocortisone. Parents members of CAH Club. Has a 2–3 cm clitoris buried under skin (clitoris often painful) and 2 perineal orifices. Behaves like a boy.
14	7	7	Ambig	M	M	46XY, incomplete diagnosis	N	Thought to be a girl until testes discovered, then named as a boy. Child is teased but parents have been telling him this is his "fate". Now they want surgery soon. Phallus 2.5 cm, two 2 mL testes, perineal urethra. Male urethra on genitogram. FSH, LH and T all normal, 17KS slightly elevated.
15	21	10	F	F	F	PAIS	Y	Female genitalia but L. testis discovered at age 10y. Not removed until 10y later. Has small breasts, sparse stage 4 pubic hair, a normal clitoris. Wonders if she is a hermaphrodite. Her **brother** (11) has a small (3 cm) penis and two 6 mL testes, no hypospadias.
16	11	4	Ambig	F	F	CAH (NSW)	Y	Ambiguity noted at birth but no attention sought for 4 yrs because mother "knew no better". 46XX, progesterone 49.7 nmom/L, testosterone 10 nmol/L. Now takes prednisolone. No interest in boys' games. Clitoris has been excised, two perineal orifices, pubic hair stage 4, early breast development, not Cushingoid. Reached menarche at 10y.
17	0.9	0.9	M	M	?	46XY gonadal dysgenesis	N	46XY, FSH and LH both elevated. Micropenis, impalpable L testis. No mullerian structures.
18	14	?	F	F	F	46X9rX)/46XY gonadal dysgenesis	N	Short stature, pubertal delay. FSH 95, LH 37.5, oestradiol 8.3 pmol/L, no mullerian structures seen. No counselling given about risk of gonadal malignancy. Patient does not know diagnosis yet.
19	4.9	1 mo	Ambig	F	M	46XY, incomplete diagnosis	N	3 cm phallus, perineal hypospadias, bilateral 2 mL testes. FSH 4, LH 2, T 6.8 nmol/L, oestradiol 67 pmol/L, male urethra on genitogram. No decision on what final sex will be yet.
20	15	14	Ambig	M	M	45X/46XY gonadal dysgenesis	Y (2)	Parents first sought advice when he was 14. Called "hermaphrodite" by a relative. Hypospadias, short broad penis, R testis 20 mL, impalpable L gonad. No mullerian structures. Short stature. No endocrine investigations. Has not been counselled about risk of gonadal cancer.

(continued)

Table 21.1 (continued)

Patient ID	Age when seen	Age at presentation	Genitalia at birth	Assigned sex	Gender behaviour	Medical condition	Had genital surgery?	Clinical details and comments
21	7	17 mo	F	F	F	CAIS	Y	Hernia containing testis discovered at 17 mo and removed. Referred to Cancer Institute which advised cancer treatment (refused). At another hospital surgeon wanted to operate (again, refused). 46XY karyotype. Female genitalia, R testis (2 mL) in groin, L inguinal scar, no gonad. Prepubertal. Her **sister** (12y, case #22) has the same condition.
22	12	?	F	F	F	CAIS	N	Sister of case #21.Was examined after her sister was found to have testes and she too had testes. No mullerian structures. Female genitalia, bilateral 6 mL testes in inguinal position. Wearing tee-shirt with "Happy Boy" logo. An older sister (14) has breasts, no pubic hair and no menses but she has not been seen by a doctor because she has no lumps in the groin. An aunt (also not seen) is married with no children and she has never menstruated. Family had not been given counselling about CAIS.
23	1.7	1.7	Ambig	M	?	Dysmorphic syndrome, probably Apert's	N	Born with micropenis (<1 cm), hypospadias and bilateral cryptorchidism. 46XY, no ultrasound. Hypertelorism, epicanthic folds, divergent squint, umbilical hernia, developmental delay.
24	5	4	Ambig	M	M/F	46XX gonadal dysgenesis	Y	Extreme poverty. At child's birth, parents were told they had a "hermaphrodite". Initially raised as a boy. Subject of gossip and object of abuse in the village (terrible experience for the mother). Taken to district hospital at age 4, then to children's hospital. Investigations showed 46XX, FSH 5, LH 57 U/L. Mullerian structures present. Was then referred to a surgical hospital. Parents expected surgeon to make child a boy but were told after the operation that he had decided to make genitalia female and that both gonads had been removed. Now has a tiny clitoris, rugose labia and 2 perineal orifices. Parents might not be able to afford oestrogen tablets.

Table 21.1 (continued)

Patient ID	Age when seen	Age at presentation	Genitalia at birth	Assigned sex	Gender behaviour	Medical condition	Had genital surgery?	Clinical details and comments
25	5	5	Ambig	M	M/F	Gonadal dysgenesis	N	Tay ethnic minority child. Noted to have atypical genitalia. Other village people completely supportive. At central hospital a technician told mother the child was a "hermaphrodite". Child dresses in a mixture of boy's and girl's clothing. Only wants to play with girls. Phallus 2.5 cm, perineal urethra, R gonad has a hard upper pole and a softer lower pole. L gonad impalpable.
26	10.6	3	Ambig	F	F	CAH (NSW)	Y (2)	Born with darkened and rugose labia but clitoris was considered normal. When later it grew, attention was sought. Serum 17OHP 70.9 nmol/L, 46XX. Now on steroids. Feminine, slender girl. Rugose labia. Clitoris (glans and shaft) completely buried under skin. Two perineal orifices. PH3, breasts stage 1. Parents belong to CAH Club.
27	9	Birth	Ambig	F	F	CAH (SW)	Y	On hydrocortisone and fludrocortisone therapy for CAH. Five adrenal crises in 1st yr, none since. Good cosmetic result from genitoplasty. Parents belong to CAH Club.
28	5	Birth	Ambig	F	M/F	? PAIS	N	Midwife informed parents that child was a "hermaphrodite". Parents thought child was female. Has only very slight clitoral enlargement. Urogenital sinus. Bilateral labial gonads. 46XY, LH 3.5, FSH 7.2, testosterone 0, no mullerian structures. Final gender not regarded as settled.
29	4	3	Ambig	F	M/F	46XY, incomplete diagnosis	Y	Presented with clitoral enlargement and clitoral excision was carried out before any investigations were done. Was then treated for CAH despite lack of investigations. Later referred to Endocrine Unit and found to be 46XY. When taken off steroids, was found to have elevated 17KS (21 micromoles/d), serum testosterone 24 nmol/L, progesterone 9 ng/mL). Normal electrolytes. Has one palpable gonad (2 mL) and a single perineal orifice.

phrase, *ái nam ái nữ*, meaning both 'hermaphrodite' and 'homosexual' was reportedly used in reference to a number of the DSD children by relatives or other villagers (e.g., patients 12 and 20), causing great distress to the parents. Recounting this experience caused the parents to weep. In two cases, (patients 25 and 28) a health worker (a radiographer and a midwife) was the first person to use this term when speaking to the parents. The term seems to be used very widely by doctors as well as the lay community.

Some patients (Nos. 3, 9 and 25), on the other hand, were beautifully supported by their local community. One of them (No. 9), a genetic female who became progressively virilised due to undiagnosed non-salt-wasting CAH, even negotiated a reversal of gender identity from female to male with the support of school friends but no medical support. He has emerged with high self-esteem and has management responsibilities despite only being 137 cm tall.

All of the patients with CAH are members of a CAH Club that was established in 1998. They reported that they found this to be of tremendous benefit and support. The group currently represents over 200 families.

Genetic counselling is not well developed in Vietnam and several families with multiple children with the same condition (patients 4, 15, 21 and 22) had not been counselled about the risk of recurrence in future siblings. Counselling about the risk of gonadal malignancy in cases of suspected 46, XY gonadal dysgenesis (cases 18 and 20) had not been given.

Several patients (Nos. 5, 6, 8, 27) had poor general health due to recurrent adrenal crises. Others with CAH became progressively virilised in a way that is rarely seen in more affluent environments. This reflects the high cost of medications that leads some parents to ration the dosage to fit their ability to pay, rather than give the prescribed amount. It may also reflect the inability of the clinic to carry out routine tests to monitor the adequacy of the dosage because the most sensitive test, serum 17-hydroxyprogesterone, is not available in Hanoi and also because the high cost of laboratory tests is prohibitive.

No clear diagnosis was available for a number of patients (Nos. 3, 10, 11, 14, 19, 23, 28 and 29) because many tests could not be performed.

Religion did not appear to play a large part in any of the decision-making about the DSD. One devout catholic family with two daughters with CAIS had consulted their parish priest who had appropriately advised a medical consultation at NHP.

The quality of the surgery that had been carried out on the patients varied widely as did the timing of genital surgery. Total clitoridectomy had been performed on two girls (Nos. 4 and 16), while others (13 and 26) had an operation that completely buried the glans, causing erections to be painful. The parents of one child (patient 24) were surprised when their child emerged from surgery a female instead of the male they had been expecting. The surgeon had not sought consent for this but nevertheless the parents accepted his judgement because he was a professional. One girl with CAIS and healthy inguinal testes was referred to a cancer hospital for chemotherapy, which the parents fortunately refused.

Parents' comments about gender behaviour were obtained in relation to 23 patients. Behaviour was considered to be gender-appropriate in 13, gender-inappropriate (i.e., the opposite of what was expected) in 5 and ambiguous (not typical of either sex) in 5. Some parents were quite concerned about their child's behaviour. Several patients (Nos. 3, 9 and 24) had changed sexes (in two, from female to male, and in one, from male to female). In four, (Nos 10, 12, 19 and 28) the gender identity remains uncertain. All parents who continued to feel uncertain about their child's sex said that it caused them great anguish. It is not possible to keep ambiguity hidden for long in Vietnam. Small boys in Vietnam wear either no pants or shorts with the crotch cut out, revealing the genitalia. Gossip in the village soon starts and is hard to stop, once started.

21.4 A Long-Term Outcome Study of DSD in Melbourne, Australia

Melbourne is the capital of the Australian State of Victoria, which has a population of five million people. Twenty-four percent of the people were born overseas (20.1% from the UK and Ireland, 8.3% from Italy, 5.3% from Greece and 5.2% from Vietnam, followed by those born in New Zealand, China, India, Germany, Sri Lanka and Malaysia). More recently, significant groups have arrived from Bosnia, Iraq, Ethiopia and Somalia. Victoria's population is predominantly urban. The health system is of a comparable standard to that in Western Europe and North America. Australian citizens and permanent residents have universal government-sponsored health insurance as well as optional private health insurance and a pharmaceutical benefits scheme that makes most medications affordable for most people. The Royal Children's Hospital (RCH) is the largest children's hospital in Victoria.

The core team providing care for DSD patients has worked together for over 25 years and has been committed to a policy of disclosing all medical information to the parents of DSD infants since 1984 and to the patients themselves since 1996. Throughout the 25-year period, it has been an advocate of early genital surgery for infants with ambiguous genitalia who are to be female and currently surgery is performed in this group by an experienced expert in paediatric urology when the infants reach the age of 6–8 weeks. The group has also recommended early removal of the testes in cases of CAIS and partial 46, XY gonadal dysgenesis. The group is multi-disciplinary and includes mental health professionals and social workers who are involved with most families. RCH was also involved from the early 1980s in establishing support groups for patients with CAH and AIS (Warne 2003). The clinic has published two widely-used parent information books (Warne 1989, 1997).

The aim of this study was to assess the long-term psychological, sexual and social outcomes of DSD patients compared with two matched control populations. The original manuscript was published in the *Journal of Pediatric Endocrinology and Metabolism* in June 2005 (Warne et al. 2005), and is described more fully in Chap. 25. As this study was commenced in 2000, it predates the new classification of DSDs. The patients included in the DSD group were those with endocrine conditions, ambiguous genitalia at birth, vaginal agenesis, but did not include Turner Syndrome, Klinefelter syndrome, hypospadias, bladder exstrophy, or cloacal exstrophy.

Three different age-matched (18–32 years) patient groups completed a self-administered questionnaire of established quality-of-life and well-being inventories measuring physical health, psychological adjustment and sexuality, following a mail-out to all identified patients. The DSD group ($N=50$) and the Hirschsprung Disease (HD; a congenital disorder) control group ($N=27$) were patients who had attended the RCH, for their clinical care. The Insulin-Dependent Diabetes Mellitus (IDDM) control group was recruited from an adult tertiary hospital. The study was conducted at the hospital-based Murdoch Children's Research Institute and was approved by RCH Ethics in Human Research Committee.

The study was planned as an epidemiological study of all patients then aged 18–32 years who had had surgery at the RCH for a DSD. One hundred and forty-eight potential participants were identified through a search of specific diagnostic codes in the hospital database. Eleven DSD patients had died (nearly all from complex congenital abnormalities including heart and/or kidney defects). One patient with a minor genital malformation and five patients with hypospadias had anomalies not severe enough to warrant inclusion in the DSD group. Thirty-six patients were not included in the study as they either had an intellectual disability (2), resided in remote locations (3), or could not be located (31). Ninety-five individuals were contacted about the study of which 27 declined to participate, 68 were sent study materials and 50 returned completed questionnaires (participation rate 53%). The final DSD sample was representative of the range and frequency of conditions initially identified in hospital records.

Consenting participants received a questionnaire booklet by mail. It was described as a quality-of-life and well-being survey, investigating the long-term outcomes for people who have been treated for conditions caused by variations in sexual development before birth. The DSD group was told that their responses would help provide an understanding of how medical treatment and clinical management has affected different areas of their life. The HD and IDDM groups were informed that their responses would provide a useful comparison. The self-administered questionnaire collected socio-demographic information, along with established inventories measuring physical health, psychological adjustment and sexuality. The following is a list of the measures used. General health: Rand-36 Health Status Inventory; Interpersonal problems: Inventory of Interpersonal Problems (IIPP); Personality: Eysenck Personality Questionnaire Revised (EPQR); Self-esteem: Coopersmith Self-Esteem Inventory (SEI); Anxiety: State-Trait Anxiety Inventory, Form Y (STAI); Trauma symptoms: Impact of Event Scale – Revised (IES-R); Depression: Beck Depression Inventory, Short Form (BDI); Gender identity: Personal Attributes Questionnaire (PAQ) and The Bem Sex Role Inventory – Short Form (BSRI); Body Image: Body Parts Satisfaction Scale (BPSS); Sexual Awareness:

The Sexual Awareness Questionnaire (SAQ); Sexual Function and Satisfaction: Individual items were borrowed and modified from various other inventories.

At the time of data collection, mean age was 25 years (SD 4.0) with a range from 18 to 32 years. In the DSD group, there were proportionately more females than in the combined control group ($OR = 3.1$, 95% $CI = 1.3–7.2$; $p < 0.01$). There were no significant group differences on age, education, or sociodemographic variables.

Analysis for measures of psychosocial well-being in the DSD and control groups showed no differences on physical or mental health, depression, current anxiety, neuroticism, psychoticism, or stressful life events. The DSD group reported lower self-esteem ($p < 0.01$) and higher trait anxiety ($p < 0.05$) than the HD control group. In the DSD group, extraversion scores were higher than in the IDDM control group ($p < 0.01$). In comparison with the HD group, the DSD group patients reported more interpersonal problems on (IIIP) total score ($p < 0.05$).

Analysis based on psychosexual measures showed that the combined control group was more satisfied with size and appearance of their sex organs than the DSD group ($p < 0.05$). There was a group-by-gender interaction that showed DSD males to be the only group reporting they were 'somewhat' dissatisfied with size ($p < 0.05$) and appearance ($p < 0.01$) of their sex organs. The DSD group reported they were satisfied with their overall body appearance, although the HD control group was more satisfied ($p < 0.05$). The DSD group obtained lower scores than HD on the sexual consciousness subscale of the SAQ ($p < 0.05$) and DSD females had lower femininity scores than control females ($p < 0.05$), but there were no other group differences on the PAQ, BSRI, or SAQ. Sexual activity was defined in the questionnaire as behaviours from self-stimulation or masturbation, foreplay (arousal with partner), to actual intercourse. The DSD group was less likely to experience orgasm than the combined control group ($p < 0.05$), tended to experience more pain during intercourse ($p = 0.06$), and had more difficulties with penetration ($p < 0.01$). In comparison with the DSD group, both control groups were more likely to have had sexual activity several times or more a week ($p < 0.05$). Controls and DSD groups did not differ in level of sexual desire or self-reported enjoyment of sexual activities.

What these results show is that there were very few differences in the level of psychosocial well-being and psychosexual well-being between a representative group of adults with DSD and two age-matched control populations. Where there were differences, they were mild. The control groups were appropriate in that one group had had major surgery early in life, long-term follow up, and some subjects had ongoing medical problems. The IDDM group had a long-term medical condition requiring daily attention, frequent contact with endocrinologists over an extended period, and concerns about the effects of the disease on sexual health.

The DSD group included many who had had surgery for ambiguous genitalia. The significant thing is that this surgery was carried out when the patients were very young. For nearly a decade, concern has been raised that the policy of performing surgery early denied the individual the right to choose his or her own gender. This is mainly the concern of individuals for whom the long-term outcome had been poor, especially those unhappy with their gender identity. They claim, based on their contacts through patient-advocacy groups using the internet, that the proportion of patients with gender identity problems after early surgery is high. In our study population, only 2 out of 50 people (one with CAH and one with PAIS) changed their gender from female to male and another person with 17β-HSD deficiency who was assigned female, now wishes to be identified as male, female, transgender and intersex. One person with CAH was assigned female and did not report identifying as male or female. Ninety-six percent of our DSD study population continued to identify as the gender assigned when they were born. Genetic females with CAH rarely develop a male gender identity (Meyer-Bahlburg et al. 2004) and only do so when there has been a delay in the commencement of glucocorticoid replacement and prolonged exposure to androgen excess during childhood. Genetic males with ambiguous genitalia due to PAIS, testosterone biosynthetic defects, or gonadal dysgenesis appear to have a higher probability of developing a male gender identity (Melo et al. 2003; Schober 2001; Reiner et al. 1999) than the virilised females with CAH, and the risk of major problems will be greatly reduced if they are assigned as males from the beginning.

Our results indicate the need for improved treatment and sexual counselling for women with DSD to avoid difficulties known to occur with sexual intercourse following vaginal surgery. The surgery required to achieve this is minor. In part, however, difficulties experienced by women with CAH appear from other reports relate to lowered libido. The extent to which this can be ameliorated by better counselling and more precise hormone replacement therapy remains to be seen. We also found that DSD patients who were assigned male had a high rate of urological problems (wetting, poor stream, infections) that should be avoidable with better surgical techniques now available.

21.5 Discussion

How do parents decide what to do when the sex of the child is uncertain? The decision about the sex of a newborn baby is not, under normal circumstances, a complicated or difficult one; it is based on a fairly cursory inspection of the genitalia. The same applies when the baby has a DSD condition. The parents generally perceive the infant's appearance as being predominantly male or predominantly female and decide accordingly. There may be some bias involved, so if they are hoping for a boy, they will be more likely to interpret any enlargement of the phallus as indicating a male sex. Depending on the training of the birth attendant, any variant anatomy may or may not arouse suspicion of a medical condition needing further investigation and treatment. In Vietnam, some parents with little education saw what in the West would be recognized as ambiguous genitalia as a disorder of the urinary opening rather than as a disorder of sexual development.

How do parents decide what to do when they realize that the child does have ambiguous genitalia? In situations of poverty, they will consult whoever is closest at hand, such as the village traditional healer or health worker, or the village elders, and they will receive a wide range of opinions before they go further afield and risk incurring expense. The Western-trained doctor will be the last in line, which means that much of the grieving will have already been done before the family sees the doctor. In underdeveloped countries, referral paths are often lacking and parents can waste much time in following up incorrect advice.

Is it good or bad to delay surgery to correct ambiguous genitalia? What does the evidence indicate? We have presented evidence that delaying surgery until late childhood or adolescence leads to greater unhappiness. In India, all patients old enough to have made the decision for themselves to have surgery said they wished the decision could have been made for them when they were infants. In Australia, where early surgery is practised, only 2 of 50 subjects changed gender in adult life and two others did not answer the question about gender, for whatever reason. Quality of life for the remaining subjects was good and did not differ substantially from that of two age-matched control groups. We take this as evidence supporting a policy of early surgery, although further modifications to policy are needed to prevent errors to an even greater extent.

Is full disclosure of information always in the best interests of the patient? We believe that parents and patients are entitled to the truth, presented to them in a way that they can understand. This is not simple to achieve and the onus is on the clinicians who understand the local culture and who are sensitive to the needs of individual parents and patients to make every effort to communicate in a fully effective way and to ensure that the correct message has been received.

The long-term outcome of DSD is, from our studies, qualitatively different for patients managed in Western vs Eastern settings. Most of the difference is explained by poverty and poor education. The lack of equity in the availability of medications and services is unacceptable and strenuous efforts are needed from both the rich countries and the health administrators in the poor countries to achieve better outcomes for the poor.

Is there one ethical framework that applies to all societies, or does each society has its own internal ethical framework? We have only touched the surface of this complex subject, but our view is that people everywhere share similar ethical values. The extent to which these are observed in practice, however, is influenced by religion, culture, education and poverty. It is difficult to show the same respect for the needs of every individual when there are 200 patients to be seen in a 3-h clinic; decisions are made on the run and the chance of making an incorrect decision rises accordingly. The challenge is to ensure that change occurs and that resources are distributed in ways consistent with equity and justice.

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Medical Management of Adolescents and Young Adults

22

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22.1 Introduction

The transition in adolescence from a protected and shielded childhood to the wider world of adulthood is a testing time even for children without a DSD, but considerably more complex for patients with DSD. In this chapter we highlight the existential issues, as well as the major medical issues that need management in boys and girls as they become men and women.

22.2 Existential Issues

Adolescents with DSD face a huge range of social and psychological issues over and above the need for treatment (if possible) of their abnormal genital tract (Table 22.1). Many patients reaching adolescence will have low self-esteem and negative body image. Issues relating to their clinical care have the potential to have a negative impact. Efforts to avoid these events are now recognised. Avoiding medical photographs and avoiding repeated genital examinations or discussions with trainee doctors or medical students about the young patient will help to avoid the sense of 'being different' or a 'freak'. The opportunity to discuss their diagnosis and to have counselling to help them adjust to the effects of their DSD on their adult sex life is also important.

In girls with CAH, they may have some side-effects of the steroid replacement therapy with excess weight, or even frank types of Cushing's syndrome if the cortisone doses have not been adjusted carefully enough. Girls with 46, XY DSD may experience unwanted (and frightening) virilisation, which may induce extreme anxiety if this is the first presentation of the DSD. They are suddenly confronted with a totally different view of themselves and all the uncertainties that this brings to their expectations of their life as a normal adult.

In many families, the child with a DSD has been brought up in a very protective environment. There may be over-protective parental concern about steroid treatment in CAH, or excessive secrecy about the child's gender and anatomy, so that some DSD children may reach adolescence without ever going on a 'sleep-over' or a school camp. Once the child reaches adolescence, their need for progressive independence, comes into direct confrontation with the parents' desire to maintain a protective cocoon around their 'baby'.

Poor communication by professionals, often related to their own ignorance of the issues facing the patient, may mean adulthood arrives without the right background knowledge to enable them to be comfortable with who they are. In other circumstances, the medical management may have been adequate, but too focused on the medical or anatomical issues, rather than helping

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Table 22.1 Existential issues for adolescents

Female	Male
Why me?	Why me?
Why am I different?	Why am I different?
Who am I?	Who am I?
Is the introitus large enough for tampons?	Why is my penis small?
Is the introitus large enough for sex?	Will my penis function normally for sex?
Is my vagina large enough for sex?	Will girls laugh at me?
Do I have a womb?	Why are my testes small?
Will I have periods or not?	Why don't I ejaculate?
Can I have children?	Will my testes get cancer?
Will I need 'IVF'?	Why do I have so many urinary infections?
Will my ovaries get cancer?	Why is my urinary stream poor?
Do my ovaries need to be removed?	Can I have children?
What hormone treatment do I need?	Will I need 'IVF'?
Does 'XY' mean I am a 'boy'?	Who else can I talk to?
Who else can I talk to?	

the adolescent with existential issues or ensuring the adolescent understands their DSD diagnosis. All the feedback from adults with DSD who grew up in a previous generation would suggest that counselling with adequate knowledge and moral support is one of the most important, but neglected, factors in the entire management plan for DSD patients. Sadly, the transition between childhood and adult life coincides with a transfer from paediatric to adult medical care, often creating a gap in the management plan at what is emerging as one of the most crucial times of psychological support.

In some particular conditions, overt gender dysphoria may become manifest in adolescence when this was not present or not anticipated earlier in childhood. This is well-known for 5α-reductase-2 deficiency, where babies with ambiguous genitalia and raised as females, become virilised in adolescence with early gender dysphoria and then complete gender identity transition to male behaviour (Maimoun et al. 2011). In certain geographic locations, such as the Dominican Republic (Imperato-McGinley et al. 1974; Cai et al. 1996) and the highlands of Papua New Guinea (Imperato-McGinley et al. 1991), this phenomenon is common enough to have produced local cultural changes in these communities. The frequency of the conditions in these areas is related to inbreeding, so that the autosomal recessive mutation persists. Recent evidence, however, suggests that 5α-reductase-2 deficiency may be more common than previously thought, and may have been mistaken for PAIS in some patient cohorts (Maimoun et al. 2011). This new information is a cautionary warning for medical attendants to be not only more careful in diagnosis and gender assignment in infancy, but also to be watchful for signs of gender dysphoria in early adolescents with previously diagnosed PAIS (Meyer-Bahlburg 2001, 2002; Meyer-Bahlburg et al. 2004).

Another condition where gender dysphoria may occur is in girls with 17β-hydroxysteroid dehydrogenase deficiency (Faienza et al. 2008). The suppression of foetal androgen synthesis may have been severe enough to produce female external genitalia at birth, but with pubertal testicular enlargement the gonads themselves may be palpable and uncomfortable or even painful in the inguinal region. The production of androgens may increase sufficiently to not only induce initially unwanted virilisation, but also enough to trigger a gender identity crisis and possible transition to male gender.

In patients with CAIS, gender identity is firmly female, although there will be ongoing psychological issues related to deficient hair, absent uterus and periods, as well as understanding the implications of an XY genotype in the context of a female phenotype (Ahlquist 1994; Mazur 2005).

Adolescence is a testing social environment, where long-term friendships may be disrupted by differences in personality and world-view that in retrospect may appear trivial. Cliques form and reform almost continuously as adolescents mature, with severe consequences for anyone who is 'different'. For young women with Müllerian agenesis, or CAIS, the 'feeling different' can relate to the fact that they do not menstruate. Exploring the issues, and role-playing potential responses, should this discussion arise amongst friends, is a useful step. 'Difference' can also be felt by those with a DSD by their need for daily medications (CAH, CAIS, PAIS). Recognition that a delay in puberty associated with a delay in the diagnosis of a gonadal dysgenesis may result in the young person being 'behind' their cohort in terms of the development of secondary sexual characteristics is important.

Being aware of the educational activities in which the adolescent with a DSD is participating in is useful in terms of ensuring that the young person has the knowledge to cope with potentially challenging lessons. School classes on reproductive health and biology may pose confronting challenges as classrooms are told about chromosomes and karyotypes of males and females in a rigid dichotomous manner without any recognition of the variations. This issue can extend to health and psychology classes discussing 'unusual cases' of DSD, where phenotype and karyotype are atypical.

Disclosure is a complex and multifaceted problem. Many patients with DSD report inadequate knowledge regarding their diagnosis (Migeon et al. 2002). On the other hand, patients with DSD report the process of being told their diagnosis as traumatic – with many being able to describe in vivid detail even years later the circumstances of being told their diagnosis in a manner that is similar to those who experience post-traumatic stress disorders (Grover and Loughlin 2002). In young teenagers with DSD, care needs to be taken because as friendship groups change, the disclosure of personal information can be mis-used and abused. On the other hand, older teenagers are likely to be developing close relationships and should be able to disclose to close friends at least some of the details regarding their diagnosis. Failure to do this suggests that the details are so frightening that the young person fears rejection. Identification of this degree of fear of disclosure in an adolescent is a clear indication of need for further discussion, education and referral for psychological assistance. The pattern of discussion and disclosure of the adolescent's DSD diagnosis by parents and family members is an issue that needs to be explored. As the young person seeks increasing autonomy and independence, he or she may feel uncomfortable with family members disclosing information about their diagnosis to others.

Working in the context of a multidisciplinary team enables various members to explore the young person's understandings. Although the medical records may not always make it clear what elements of the diagnosis have been explained in earlier consultations or what has been understood, asking the adolescent to explain to you as the clinician what they currently understand about their diagnosis is a useful process and ensures a clearer understanding.

Those adolescents with gay or lesbian sexual orientation are at significant risk of discrimination and bullying, and may be ostracised from their previously close friends and peers. For teens with a DSD, these problems are even more acute, as they try to come to terms with who they are and determine their sexual orientation. All of these tensions indicate the need for specialised sexual counselling during and beyond this crucial transition.

In some unfortunate patients, initiation of sex hormone replacement therapy may trigger a major crisis by exacerbating some latent gender dysphoria.

22.3 Medical Issues (Table 22.2)

Medical treatment of CAH through adolescence may be quite challenging, as pubertal growth makes the suppression of adrenal androgen production more difficult. Optimising the balance between too much cortisone, which might be associated with irregular menses and signs of Cushing's syndrome (round face, impaired linear growth and generalised obesity), and inadequate replacement, leading to increasing virilisation, may need some changes in strategy, such as a change to once-daily treatment with dexamethasone (Young and Hughes 1990). Recently, some groups have reported on the role of bilateral laparoscopic adrenalectomy as a way of lowering steroid replacement doses, as following adrenalectomy it is no longer necessary to suppress the abnormal androgen production from the adrenal glands (Ogilvie et al. 2006). It is suggested that adrenalectomy also may improve the prognosis for fertility, although long-term follow-up studies after surgery are not yet available.

For those adolescent females with streak ovaries, puberty may need to be induced with hormone treatment. The timing and rate of puberty induction has some flexibility – but ensuring that the young person feels adequate in their development with respect to their peers is an important issue. The protocols for pubertal induction vary widely, although the principle of beginning oestrogen replacement at a low dose and very gradually increasing the dose every 6 months is broadly used. Oral oestrogens, transdermal oestrogen patches or cream can be used. Compliance in the younger adolescent may be an issue, particularly when the reasons for use of hormones have not been understood by the young girl. Where a uterus is present, progestagens will need to be added. This can be usually be initiated after the first spontaneous bleed has occurred, with the option of using progestagens continuously to

Table 22.2 Medical issues in adolescent males and females

Female	Male
Steroid hormone maintenance (CAH)	Androgen supplements/ replacement
Oestrogen/progesterone treatment	Testicular biopsy to screen for CIS
Control of irregular periods	Penile augmentation/erectile
Hemiuterus	Dysfunction treatment
Streak ovary with Y chromosome (Turner)	Urethral stricture
Vaginal agenesis (Rokitansky)	Recurrent UTIs
Short vagina (CAIS)	Poor ejaculate
Introitoplasty/vaginoplasty	Possible fertility options
? removal of testes in CAIS	Recurrent epididymitis
Donor oocyte source	
? surrogate pregnancy	

avoid menstruation, or cyclically, using 14 days of progestagens monthly or in alternate months.

Assessing response to the oestrogens can be made through monitoring of breast growth and height. Bone densities together with bone age are sometimes useful to ensure optimal doses of oestrogen are being used. Given individual responses to different oestrogens, there is some benefit from trialling a few oestrogens and doses to ensure that the eventual oestrogen suits the individual. Likewise, when a uterus is present, assessment of uterine volume, uterine body versus cervical length and the development of an endometrial stripe all provide information that confirms appropriate maturation is occurring.

22.3.1 Oestrogens

The optimal dose of oestrogen for hormone replacement therapy in young women is not known. The doses of oestrogen that are recommended for the prevention of osteoporosis in women are derived from studies on post-menopausal women rather than on young women aiming to achieve optimal peak bone mass. For post-menopausal women, the following are the daily doses generally accepted as adequate for the maintenance of bone density: Conjugated equine oestrogen 0.625 mg; oestradiol valerate 2 mg; and piperazone oestrone sulphate 1.25 mg. As the attainment of peak mass is determined by several factors including exercise, calcium intake, genetics and 1, 25(OH)Vit D, these factors also need to be optimised in young women, as well as oestrogen dose.

A few studies have been carried out to determine the optimal dosage of oestrogen for women with Turner syndrome. One study (Paterson et al. 2002) showed that ethinyl oestradiol in the most commonly used doses leads to appropriate pubertal development but is insufficient to induce mature uterine shape or size in 50% of the population. A more recent study (McDonnell et al. 2003) of girls treated with a variety of synthetic as well as natural oestrogens reported more consistent uterine growth. Additionally, other work in women with TS has shown that spontaneous puberty versus induction of puberty was associated with the achievement of better bone density with no differences in other factors including calcium intake and physical activity (Carrascosa et al. 2000). Likewise, studies in women with CAIS with and without gonadectomy have also demonstrated a failure of achievement of optimal bone density – although some of this was attributed to non compliance with medications (Marcus et al. 2000).

22.3.2 Progestogens

For women with DSD conditions with a uterus, it is essential that progestogens be used. Choice of progestogen is largely determined by the presence or absence of side effects. Administration can be oral, transdermal, intramuscular, or intrauterine (levonorgestrel intrauterine system). Progesterone administration can be cyclic (e.g. medroxy progesterone acetate 10 mg daily for 14/7, dydrogesterone 10 mg, 14 days per month) or continuous, for the achievement of amenorrhoea. There are no data on 'best' progestogen, although data on minimal dosage and duration are available to ensure prevention of endometrial hyperplasia (Warne et al. 2005).

22.3.3 Fertility

For young women where a uterus is present, there is a possibility of carrying a pregnancy. For women with CAH, adequate control of adrenal hormones is necessary. The girl with a hemiuterus because of ovotesticular DSD or mixed chromosome DSD with mixed gonadal dysgenesis, referral to an experienced gynaecologist is appropriate for advice about whether a pregnancy would be possible.

In girls with streak ovaries, another important issue is whether Y chromosome-containing cell lines are present as these are known to be a potential cancer risk (Looijenga et al. 2007, 2010). Improvements in molecular and cytogenetics have shown that many children with 45X Turner syndrome have some previously unrecognised 45,X/46,XY mosaicism which predisposes the streak gonads to malignancy (Nishi et al. 2002). The current consensus for management is that these girls (any young women) should all have their karyotype tested with modern molecular techniques to detect any occult mosaicism, and if identified, prophylactic laparoscopic removal of the streak ovaries is recommended (Cadeddu et al. 2001).

For patients with 46,XY DSD being raised as girls, this is not normally an issue in adolescence, as gonadectomy is usually recommended earlier in childhood because of the cancer risk in intra-abdominal dysgenetic testes (Zielinska et al. 2007) (see Table 7.2).

By contrast, for girls with CAIS, there is significant controversy about whether the inguinal or intra-abdominal testes should be excised, as the cancer risk over a lifetime appears to be much lower than previously believed (Looijenga et al. 2007). In a previous generation, and still currently in many centres, gonadectomy is carried out in infancy at or shortly after diagnosis of CAIS (Wisniewski et al. 2000). There is now a shift to delaying this till after normal pubertal development has occurred after aromatisation of the excess androgens into oestrogen. Even then, the risk of testicular cancer in an otherwise normal testis in a patient with CAIS is similar to that of a man with previously undescended testes, where the risk is five- to ten-fold higher than in normal testes, but not so great that orchidectomy is considered necessary. The site of the testes in the girl with CAIS will influence this decision. For the girl with intra-abdominal testes, monitoring of the testes is necessary due to the 2–3% risk of malignant change. The detection of any change in size or shape of the testes is then usually enough cause for anxiety for the gonadectomy to proceed. For the girl with testes in the groin, inguinal canal or labia, their presence may be the source of pain, particularly with sexual activity leading to the decision for gonadectomy.

The other main medical issues for girls and young women with DSD relate to the gynaecological management of the introitus and the short or absent vagina, and are discussed more fully in Chap. 23.

Future fertility in a young woman with no ovaries but a full uterus or a hemiuterus may be achieved with the aid of in vitro fertilisation (IVF) technology. Oocyte donation can be from related or nonrelated women. Although we are seeing parents of infants arranging to store oocytes in the bank for possible future use by their daughters, there are considerable ethical questions around this. Some countries do not allow the parent to be an egg donor, due to the complexity of the young woman carrying a pregnancy that is effectively her sister.

In girls with Turner syndrome, the ovary may initially contain ova prior to premature senescence and the resultant loss of fertility potential. In this circumstance, the ova may be harvested prior to this time and stored for subsequent use by the patient herself. There are now case reports of cryopreservation of ovarian tissue, but it has not yet become standard therapy, as the timing of ovarian failure is quite variable and occurs in early childhood in most cases. Whether harvesting ova from infant ovaries is feasible, let alone ethical, is an issue for the future. Although the technology of cryopreservation of ovarian tissue has been undertaken for over a decade, there are only a small number (<10) of reported pregnancies arising from this technology worldwide (Meirow et al. 2005; Ernst et al. 2010) and none have been from ovarian tissue from a woman with gonadal dysgenesis. There are concerns regarding higher rates of problems in the early embryos from women with Turner syndrome (TS) (Bodri et al. 2006, 2009). An additional consideration is the increased pregnancy complication risks for women with TS. The overall pregnancy risks are thought to be 100-fold increased (Bodri et al. 2006), with reports of a 2% maternal mortality associated with aortic dissection (Practice Committee ASRM 2008; Karnis et al. 2003). Although those women with TS who have risk factors such as prior coarctation, bicuspid aortic valve or hypertension are clearly at higher risk, there is evidence that even those without any specific risk factors and who have pre-implantation and antenatal monitoring of their aortic root may still develop aortic root dissection (Karnis et al. 2003). These concerns do not apply to women with DSD who have a uterus and require donor oocytes.

In young women with Műllerian duct agenesis causing absent vagina +/or absent uterus, there is the possibility of a surrogate pregnancy, as the ovaries are usually normal (Sheean et al. 1989). Techniques for super-ovulation and harvesting of ova are now well-established, and the major remaining barrier to this treatment is moral

Table 22.3 Currently available forms of testosterone

Product	Form	How administered	Usual dose	Comment
Testosterone esters (Sustanon)	250 mg ampoule	Deep intramuscular injection	Adolescent: start with 50–100 mg/month Adult: 250 mg 2–4 weekly	Peaks and troughs of hormone level may be symptomatic
Testosterone enanthate injection	250 mg ampoule	Deep IMI	Adolescent: start with 50–100 mg/ month Adult: 250 mg 2–4 weekly	Peaks and troughs of hormone level may be symptomatic
Testosterone undecanoate (Andriol)	40 mg capsule	Oral	Adolescent: 40 mg once or twice daily. Adult: 80–120 mg twice daily	Efficacy variable
Testosterone undecanoate injection (Reandron 1000)	1,000 mg in 4 mL	Deep IMI	Adult: 4 mL initially, and after 6 weeks, then every 10–12 weeks	Delivers relatively constant hormone levels
Testosterone pellets	200 mg pellet	Subcutaneous implant	400–800 mg every 6 months	Risk of infection and extrusion of pellet
Testosterone gel	10 mg/g, 5 g sachets	Transdermal gel	Adult men: 5 g applied at night, adjusted according to testosterone levels	Sexual partners may be exposed to effects of testosterone through contamination
Testosterone transdermal patches	2.5 and 5 mg patches	Transdermal patch	Adults: 2.5–7.5 mg/24 h	

and ethical. This remains a controversial area, with debate about financial reimbursement for the woman carrying the pregnancy. However, as attitudes to assisted reproductive technologies evolve, this option is likely to become more frequently exercised. In young women with 46,XX DSD and complex anomalies, fertility and the option of a pregnancy may be confounded by their other anomalies. Extensive previous surgery to correct bladder or cloacal exstrophy may result in pelvic adhesions and infertility. Assisted reproductive techniques can be used to overcome this. Renal function and stomas may pose additional pregnancy-related challenges, and the mode of delivery will need special consideration – including the risk to bladder and bowel sphincters with a vaginal delivery versus the challenge of a caesarean section in the presence of altered anatomy.

Genetic counselling for women with DSDs who have fertility (CAH, vaginal agenesis – with surrogacy, bladder exstrophy, cloacal exstrophy) is important to allow the opportunity to discuss the risk of anomalies in the offspring.

22.3.4 Male

In many DSD patients raised as males, the dysgenetic testes may produce some androgens at puberty; first, it is difficult to predict beforehand whether this will be sufficient. Some boys may need full induction of puberty while others may only need supplemental androgen treatment (Table 22.3).

Once puberty is advancing, there needs to be consideration of whether the underlying testicular dysgenesis is likely to predispose to carcinoma in situ (CIS) and subsequent testicular cancer later in early adult life. A sensible plan is to recommend testicular biopsy in middle-to-late adolescence to determine whether CIS is present or not (Cools et al. 2006; Hoei-Hansen et al. 2005; Levin 2000). If the biopsy is negative, then regular surveillance with ultrasonography is probably sufficient. However, if CIS is identified, then a decision needs to be made about management. Some doctors may recommend sperm storage (if this is possible) prior to either irradiation of the gonads (utilising the exquisite sensitivity of germ cell tumours to irradiation) or orchidectomy. If the latter is chosen, then insertion of prostheses along with full hormone replacement will be needed. It is not yet clear in follow-up studies which one of these options is the best, and of course, it may vary between the lad himself and the doctors.

Young men with a micropenis secondary to hormone deficiency/resistance, a primary isolated genetic anomaly, or associated with complete anterior abdominal wall defects (e.g., bladder exstrophy and cloacal exstrophy) may be seeking penile enlargement or substitution. In men with penile agenesis or loss from trauma, a surgically-created phallus is the only option (Ricketts et al. 2011). For micropenis, however, reassurance about otherwise normal sexual function may be sufficient.

Common problems in young men with DSD are the complications arising from hypospadias surgery (Jones et al. 2009). Where the urogenital sinus opens between the labioscrotal folds, there are increased risks of urethral stricture and meatal stenosis following construction of a very long neourethra from skin +/− buccal mucosa. After hypospadias repair, the neourethra is relatively narrow, and during micturition urine may be forced into the vaginal remnant, causing progressive enlargement. The latter allows stasis to develop in the diverticulum with colonisation by bowel flora, leading to recurrent urosepsis. We once treated a boy with 46, XY DSD with MGD who had not been diagnosed at birth despite hypospadias and had 100 operations for urethral dilatation of a recurrent stricture before it was realised that he had a DSD with a large vaginal remnant filled with infected urine. Excision of this remnant led to immediate resolution of his intractable problem.

Over the years, some boys have required formal vasectomy to prevent recurrent retrograde spread of faecal organisms to the epididymis. The vasectomy may only be required on one side, but in many boys, the urogenital (vaginal) remnant itself needs to be excised to prevent urinary and/or epididymal chronic sepsis. Where this is needed, the vas deferens, if present, nearly always is found draining into the cavity, so that vaginal remnant excision is tantamount to bilateral vasectomy. Is this good or bad? In the authors' view this is usually good, as ejaculation is hardly ever normal if the vas is connected to a vaginal cavity, as the seminal vesicles are abnormal, and there is chronic sepsis in the cavity. By contrast, disconnection of the vaginal cavity from the posterior urethra may enhance fertility potential (albeit needing medical assistance) by protecting the epididymis from chronic sepsis, thereby destroying its crucial storage and maturational functions for sperm.

Recently we have begun disconnecting the residual female genital tract from the male urethra laparoscopically without excision. This achieves the aim of avoiding recurrent urosepsis and epididymitis in any remaining testis, but preserves the female organs should the patient wish to change gender later in life. Whether this is an advance in medical management remains to be seen, but already seems to be an advance from an ethical perspective.

Table 22.4 Holistic management through adolescence

Psychological counselling
Sexual counselling
Establishing appropriate adult transition
(a) Medical management
(b) Cancer screening
Support Groups

If the remaining testicular tissue is in a scrotal position, and therefore functioning at the correct temperature (33°C), and there is sufficient androgen function, then production of spermatozoa is possible.

Even if the plumbing of the vas deferens is abnormal as described above, aspiration of mature sperm from the epididymis or testis may allow fertilisation of an ovum. This technology holds promise for many young men with DSD, and is a major advance compared with the bleak fertility prognosis in the past.

22.4 Holistic Care Through Adolescence (Table 22.4)

It is not quite 60 years since Lawson Wilkins first described congenital adrenal hyperplasia as a cause for genital anomaly (Wilkins 1965). This triggered rapid advances in medical and surgical treatments for an expanding range of DSD, but with not all treatments equally successful. As in all areas of advancing knowledge, learning something new is by trial and error, and the management of DSD is no exception (Brain et al. 2010; Ahmed and Rodie 2010). As we have now had several waves of young adults emerge from different eras of medical treatment, we are just starting to appreciate the strengths and weaknesses of some therapies, mostly by feedback from the patients themselves.

The message from past patients is clear: we need holistic care that is medically sophisticated as well as non judgemental, and on-going through adolescence into adult life. We are establishing psychological and psychiatric counselling as part of our regular DSD treatment plan through childhood, but have yet to develop a formal structure for adolescent and adult sexual counselling. Importantly, there are relatively few places even in the developed world, where there is formal transition to adult care by experts, for ongoing medical and psychological treatment and cancer screening.

Perhaps most importantly for the management of adolescents and young adults is the establishment of a

Table 22.5 Useful websites for information on DSD

www.sgan.nhsscotland.com
www.sickkids.ca/childphysiology/cpwp/Genital/genitaldevelopment.htm
www.aisg.org/26_PARENTS.HTM#Books2
www.mrkh.org
www.youngwomenshealth.org
www.turnersyndrome.org.au
www.dsdguidelines.org
www.rch.org.au/cah_book/index.cfm?doc_id=1375
www.rch.org.au/publications/CAIS.pdf

number of patient support groups, where patients can meet their peers. In the 1980s, support groups were established for parents of children with DSD, with the CAH Support Group being one of the first. Now what is occurring is networks of young adults with DSD, aided by the internet, which has enabled people with rare conditions to meet others with the same condition (Table 22.5)

22.5 Conclusions

As with other chronic diseases of childhood, the management of DSD has improved sufficiently for there now to be large numbers of adolescents and young adults with reasonably well-defined disorders. Their medical and psychosocial management is advancing, but there remain deficiencies, particularly in transition to adult care. Along with advances in molecular diagnosis, this is likely to be one of the major sites of improvement in care in the next decade.

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Gynaecological Management

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23.1 Introduction

The aim of gynaecological care of young women with a DSD is for the person to reach a healthy, happy state of well being, with the capacity to have positive relationships, including the potential for enjoyable and fulfilling sexual relationships. The desire for fertility is a possibility that may be more difficult to fulfil with a DSD diagnosis, but this too requires consideration.

These outcomes are dependent on a number of factors apart from those directly relating to the features of the specific DSD or the direct medical and surgical care. Some of these other prerequisites include having a positive self-esteem and body image, and the absence of depression. Thus examining the gynaecological management issues and the outcomes cannot be done in isolation.

Although this chapter deals primarily with the management of adolescents and young women with DSDs, there are earlier events and medical experiences that may have a negative impact – and thus, as a gynaecologist some effort to ensure that optimal parental information as well as the avoidance of potentially traumatic events in childhood is also part of the gynaecological input.

Some of the issues described here may be undertaken by clinicians and health professionals other than gynaecologists. The gynaecology team at Royal Children's Hospital, provides gynaecology care to the paediatric and adolescent age group for a range of different problems and routinely explores psychosocial aspects of the young person's life as an integral part to the provision of this clinical service. The gynaecologists are therefore comfortable to provide some of the psychosocial discussions and to undertake basic sexual counselling. This has enabled us to identify those in greater need, or to identify when the young woman is ready for further psychological input – before a referral is made to the limited psychology services that are available within the public hospital setting. In other places, psychologists may be more readily available to explore the psychosocial adjustment in young people with DSDs; sexual counsellors may do all of the discussions regarding sexual activity, or this may be shared between the psychologist and sexual counsellors. Another alternative is that a nurse practitioner linked to a DSD service may provide some of the primary psychotherapeutic support and be able to trigger the relevant referral to psychologist or sexual counsellors when indicated. The important issue is that the topics raised here are relevant for the long-term wellbeing of young women with DSDs and someone needs to be comfortable in ensuring that these issues are explored.

23.2 Neonatal Period

23.2.1 Talking with Parents

Parents, when confronted with trying to understand the impact of a DSD on their baby are trying to integrate a complex range of information which includes aspects regarding long-term outcomes. Although paediatricians

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and paediatric surgeons who care for the neonate are also likely to be involved in the care of young children and young adolescents, most do not have involvement in the reproductive health and sexual aspects of young or adult women with these diagnoses. Thus, the insights and perspectives regarding teenagers at school, their interaction with peers and responses to peer pressure around issues relating to menses and relationships, and for young women becoming sexually active may be outside their clinical experience. Parents often ask questions about – 'What will it be like for our baby (if she is raised female) when she grows up', 'How will she feel when she doesn't have periods when her friends do? to questions around 'How different will she be to her friends'? 'Will she fit in?' 'Will she be a normal girl?' 'How will she cope?'

To be able to respond to these questions, careful answers are required that acknowledge the differences that are present in all children. Additionally, some discussion with parents regarding normal variations in behaviour of children and young people is essential. For some girls with DSDs, the likely behaviour patterns are a little more predictable, as girls with congenital adrenal hyperplasia (CAH) are somewhat more likely to be participate in 'tomboy' play activities (Berenbaum and Bailey 2003) – but remembering that girls can also be 'tomboys' without it signifying any underlying DSD.

Other behavioural aspects are more difficult to predict as there is such a wide variation in 'normal'. Some groups of adolescent girls talk about periods and others don't – so the question of whether their daughter will tell friends about 'not having periods' (if there is an absent uterus in the specific DSD diagnosis) is very dependent on specific teenage friendship groups.

Part of parental concern, but not always voiced spontaneously, is regarding the future potential of their child to be able to undertake sexual activity as an adult. Clearly any positive sexual activity is very dependent on finding the right partner. For people with DSDs, the diagnosis itself does not preclude the possibility of having a successful sexual relationship. Reminding parents that many factors influence sexual experiences and pleasure is part of this discussion.

Speaking to parents, from a context of having cared for adolescents and adult women with similar diagnoses to that of their baby, offers some perspective and reassurance for the future.

23.2.2 Surgical Input

An additional role that a gynaecologist can play in the neonatal period is in supporting the paediatric surgeon. Although in theory gynaecologists could undertake the surgery in the infants – most gynaecologists have had no training in genital surgery in babies. In contrast, paediatric urologists and surgeons undertake surgery to the baby with severe hypospadias and are thus familiar with the anatomy relating to the erectile tissue, nerve and vascular supply of the glans. Despite this, the gynaecologist can have an input in terms of 'fine tuning' the genital surgery. Additionally, it is beneficial for the gynaecologist to understand the surgical techniques used to assist in understanding the potential problems that may be present in adolescence and adulthood.

Aiming for the creation of labia minora in the infant with virilised genitalia, has been incorporated into the genitoplasty by some paediatric surgeons since the 1980s (Kogan et al. 1983). The creation of a clitoral hood has not been mentioned in papers describing the operative technique of genitoplasty; yet, this too can be readily achieved at the time of the feminizing genitoplasty. To date, assessment of the presence of the clitoral hood has been omitted from the standardized genital assessment tools that have been developed to assess long term outcomes of this surgery (Creighton et al. 2001; Nordenskjold et al. 2008).

23.2.3 Timing of Surgery

There is considerable debate regarding the timing of genital surgery. It is clear that there are arguments for and against this early surgery. As the gynaecologist in a team of clinicians caring for young people with DSDs, one of the gynaecologist's responsibilities is to ensure that optimal surgical outcomes as measured by long-term outcomes are occurring in that centre.

In some countries, early surgery undertaken for virilised genitalia has not included the introitoplasty or vaginoplasty. Some have argued that the vaginoplasty should be omitted in early surgery due to the high rate of further surgery (Creighton 2004). Thus rather than aiming for a one-stage procedure, acceptance that genital surgery will be two-stage, with the vaginal component delayed till adolescence (Creighton and Minto 2001), has been advocated.

When this has not been done for those girls with a uterus (most frequently those with CAH), medical concerns arise with the onset of puberty as to whether the menses will be able to adequately drain through the urogenital opening. Medical pressure then mounts to undertake surgery at 11–13 years of age. This is not the ideal age to undertake genital surgery. The 11–13 year old girl tends to be embarrassed and uneasy about her genitalia and is unlikely to be mature enough to fully understand why the surgery is required. An option is to suppress the menses – but this option then generates further medical consultations regarding menstrual suppression, intervention with medications, (either progestogens, the continuous oral contraceptive pill or the gonadotrophin-releasing hormone agonists) with the possibility of side effects from these medications and further medicalisation of the girl.

Research on males with hypospadias has indicated that surgery undertaken at an age when the boy is able to remember the surgery is more likely to have a negative impact on body image, self-esteem, and their psychosexual outcomes. These findings are independent of the actual anatomical and functional outcomes (Mureau et al. 1995; Jones et al. 2009). The potential psychological impact of delayed surgery has not been explored for women who undergo feminising genitoplasties, although Nordenstrom reported that of women with CAH who had undergone clitoral surgery 20/29 advocated early timing of surgery (Nordenstrom et al. 2010).

Data from the UK have revealed that when young women who had feminising genitoplasties were assessed, 89% were found to require further major surgery (Creighton and Minto 2001; Creighton et al. 2001). A similar study in Melbourne (Lean et al. 2005) and in Hanoi (Grover et al. 2010) revealed that although many would require dilatation only a small number would require further surgery – most of which was likely to be minor involving a revision introitoplasty. It is unclear whether this difference reflects the population studied or the initial surgery (the surgical technique and expertise of the original surgeon) or all of these factors. In both Hanoi and Melbourne, the provision of feminising genitoplasty surgery is at a single hospital in each city and the surgery is undertaken by a small number of experienced surgeons. In Hanoi, the study population was girls ($n=40$) attending for the annual CAH meeting day /clinic, whereas in Melbourne girls >12 year old ($n=32$) who agreed to be examined in clinic made up 50% of all girls who had had genitoplasties in the relevant time period and these girls were considered representative of the total population cared for at the Royal Children's Hospital, Melbourne. In contrast, the study population reported by Creighton (Creighton et al. 2001) consisted of women from all over the United Kingdom recruited from the CAH support group or who had been seen in the London clinic, which is a specialized adolescent/adult clinic with referrals from all over the UK, thus representing quite a different cohort.

Thus for some centres, where research has demonstrated poor long-term outcomes, it may be wisest to advocate for delayed surgery. Alternatively, where the research outcomes demonstrate good results, then there is a place for supporting the early surgery.

23.2.4 Reproductive Prognosis

An additional role of the gynaecologist in the neonatal period exists in terms of offering information regarding the future genital capacity of reproductive tract structures present in the infant. In some babies with DSD, there may be a combination of male and female anatomical structures present. Previously, some of these structures were thought to be remnants or vestigial (Davies et al. 2004) and thus removed.

In the past, where a decision was made to raise a baby as a male, this would have led to the removal of any structures which were female. Yet these structures, in particular, a unicornuate uterus, are quite capable of successfully carrying a pregnancy. Thus in a condition such as mixed gonadal dysgenesis, where there may be a unicornuate uterus present on one side, with an ipsilateral streak or nonfunctioning gonad, there may be a contralateral gonad producing testosterone, resulting in the external genitalia being partially virilised, although often with hypospadias present. For those babies where a decision is made to raise the child as a male, the question is whether the uterine structure should be removed. Although the majority of these infants if raised male are likely to identify as male when adult (Cohen-Kettenis 2005; Szarras-Czapnik et al. 2007), there are nevertheless some reports of dissatisfaction with gender of rearing. In these young people, preservation of the uterus would enable the possibility of carrying a pregnancy (with donor egg) should they chose to change their gender in adolescence. It would be appropriate to ligate the lower end of the vagina to prevent retrograde urine flow into the vagina, but removal of the uterine structure can be delayed till the gender identity of the individual has been clarified during adolescence.

23.3 Childhood

During childhood there is very little need for significant medical or surgical input. Nevertheless it is a time when gentle education may begin and encouraging this possibility with parents is appropriate. The opportunity to raise issues relating to diversity can be incorporated into responses. When families are having discussions about growing up, the fact that everyone is different can be incorporated into those discussions. When discussions occur about people having babies, the possibility that not everyone can have a baby, that some people need help to have babies, that other people chose to adopt, and others decide not to have babies can all be raised in a non threatening gentle manner.

During childhood, it is important to ensure that traumatic medical experiences are avoided. In the past, medical photographs were often taken with the young person standing naked for the picture. These experiences are often recounted by the young women when they are adults as unpleasant events. They have the potential of having a negative impact on self-esteem and body image.

Genital examinations are also often recalled as negative events subsequently impacting on future sexual experiences. These genital examinations often used to occur with several observers (junior doctors or medical students) present. In some settings, these genital examinations may also have included a vaginal examination. As no surgery to the genitalia should be required in childhood (after the possible genitoplasty undertaken as an infant), these examinations are unnecessary. Although it has been argued that a genital examination can give an indication of compliance with medications in the setting of CAH, there are alternative means of assessing adequacy of cortisone dosage (by blood tests, measuring blood pressure, looking for evidence of a cushingoid appearance, or hirsutism and pigmentation) which are far less intrusive.

As the long-term aim is for the young person to have a positive self-esteem and body image, the genital examination in a young person who does not understand why it is being done is usually not a positive contribution.

23.4 Adolescence

23.4.1 General Issues

An advantage of providing an adolescent gynaecology service is that it provides an ideal opportunity to begin to transition the care from one where the main communication is with the parent, to one where the focus of communication is with the adolescent. As this is the age when transition to autonomy begins to occur it is opportune to work towards a consultation occurring without parents. Studies suggest young people are not well informed about their diagnosis nor are they satisfied with their knowledge (Migeon et al. 2002; Nordenskjold et al. 2008) and an effort must be undertaken to ensure that the young person herself understands her diagnosis.

Psychotherapeutic groups for young women with DSD have led to the identification of a number of themes that are useful to explore (Grover and Loughlin 2002). Young women with DSD often report feeling different from their peers; relationships with peers and partners may be difficult due to concerns that their diagnosis should be a secret; the need for open disclosure; many report being informed of their diagnosis as a traumatic event – with features suggestive of a post-traumatic stress disorder; and fertility and infertility is an issue that becomes more prominent as they become older adolescents. The psychotherapeutic groups are reported as positive experiences by many of the young women. Unfortunately, there is no work to clarify the respective benefit of meeting others face to face, versus establishing contact via internet-based support groups or by email contact. The opportunity for the young women to be able to make contact or speak to others reduces the isolation and sense of being alone and different.

Some of the anxiety relating to genital appearance may stem from the fact that for some young women, their genitalia were repeatedly examined in childhood. Over the last 15 years, a policy of not examining the genitalia in young children and adolescents until the young woman herself is interested in looking, with the aid of a hand-held mirror and consents to this being done, appears to have led to a decline in the anxiety about genital appearance in our patient population.

Hormonal treatment to allow the progression through pubertal changes and gain secondary sexual characteristics is required for a number of adolescent women with DSD.

Discussion around relationships, peer groups and establishing if the teenager is undertaking similar social activities to her peer groups is part of this assessment. Some exploration of what the young woman understands about her diagnosis and what she has told others also gives some indication of how comfortable she is with her diagnosis. An adolescent in her mid to late teen years has usually formed close friendships, and disclosure to close friends of some of her diagnosis – whether it is that she has no periods, or that having babies will be difficult can usually be interpreted as a positive sign of adjustment to her diagnosis. The older adolescent who has not disclosed any information about her diagnosis to anyone, suggests that for the young woman, the diagnosis is such an enormous secret and so shameful that it can't be shared. If referral for psychological support has not occurred prior to this point, then this signifies the need for such intervention.

Fertility and the issue of infertility are topics that are normally raised by gynaecologists. For some women with DSDs, the presence of a uterus means that the potential to carry a pregnancy exists. For women with a uterus but with a DSD diagnosis, this usually means that the gonads are non-functioning, hence a donor egg is required for a pregnancy to occur (e.g., XY or XX gonadal dysgenesis, mixed gonadal dysgenesis, ovotesticular DSD). For some diagnoses, in particular for those with Turner Syndrome, despite the presence of a uterus, there may be substantial risks associated with carrying a pregnancy (Bondy 2007) which need to be discussed with the young woman. Another group of women who benefit from discussions regarding fertility are those with uterovaginal agenesis, where the young woman has functioning ovaries, but no uterus (and potentially, initially, no vagina). These women have the possibility of using a surrogate to carry their pregnancy. To date, although there has been some research into uterine transplant (Brannstrom et al. 2010), no successful transplantations have occurred.

23.4.2 Genital Appearance and Function

Where a feminising genitoplasty has been performed for those born with some virilisation of their external genitalia, clitoral, introital and labial surgery may be required.

Reports on the long-term outcomes of this surgery have often failed to describe the exact surgical technique that was used or the experience of the surgeon. The techniques used have changed over time ranging from clitoridectomy (or amputation), clitoral recession to girth reduction procedures (Lean et al. 2007). Some studies reporting on the outcomes of surgery include data on the experience of the surgeon, in terms of the number of different surgeons who have operated on the patients in the cohort (Alizai et al. 1999; Lean et al. 2007; Nordenskjold et al. 2008), but the expertise of the surgeons is not mentioned by others (Creighton et al. 2001; Minto et al. 2003b; Kuhnle et al. 1995).

Reports on the outcomes of feminising genitoplasty are mixed, and it has only been in the last decade that attempts to use a standardized approach to the assessment of the cosmetic and anatomical outcomes has occurred (Creighton et al. 2001; Nordenskjold et al. 2008). Analysis of anatomical and cosmetic outcomes include assessment of clitoral size (see Table 23.1), introital size, and labial appearance.

Creighton reported outcomes of 44 women with poor cosmetic outcomes in 41%, and with 89% requiring further major surgery to use tampons, or to have sexual intercourse (Creighton et al. 2001). In contrast, Lean et al. reported on 32 patients with 6% poor cosmetic outcomes (Lean et al. 2005). In this series, two-thirds of all the surgery was undertaken by one surgeon with a specialized interest in this area.

Another critical perspective on surgical outcome, which has been omitted in many studies, is that of the patient self report (see Table 23.2). It is important to note that without surgery, there are concerns with satisfaction regarding clitoral size – despite the fact that much discussion in the literature has centred around the outcomes of surgery, ignoring the fact that the condition itself has resulted in a difference in appearance of the genitalia, and the question should be whether the outcomes of surgery and postsurgical satisfaction are higher than amongst those who have not had surgery.

Table 23.1 Clitoral size in patients who had undergone clitoral surgery

	Normal	Absent	Small	Large	Very large
Alizai (Alizai et al. 1999)	7/14	1/14	4/14	1/14	
Creighton (Creighton et al. 2001)	26/44	3/44	3/44		9/44
Lean (Lean et al. 2005)	24/32	4/32	3/32	1/32	
Nordenskjold (Nordenskjold et al. 2008)	11/38	4/38		19/38	

Table 23.2 Clitoral size judged by women with CAH with and without surgery and controls (Nordenskjold et al. 2008)

Clitoral size according to the woman	Controls $n=60$	Women with CAH, had clitoral surgery $n=38$	Women with CAH, no clitoral surgery $n=24$
Too large	0	8/38	13/24
Normal	60	19/38	11/24
Too small	0	6/38	0/24

23.4.3 Vaginal Surgery

Vaginal surgery, in the setting of virilised genitalia, likewise has shown mixed results. Many report the need for repeat vaginal surgery in the setting of a planned one-stage feminising genitoplasty procedure (Crouch et al. 2008; Stikkelbroeck et al. 2003; Alizai et al. 1999). Despite the need for repeat surgery, some research has shown that this does not necessarily result in a negative long-term outcome (Stikkelbroeck et al. 2003).

Satisfaction with vaginal size (using a 5-point scale) in a cohort of women with CAH who had had surgery ($n=37$), compared to a group who had not had surgery ($n=20$) and compared to a control population ($n=60$) has been reported by Nordenskjöld (Nordenskjold et al. 2008). Of controls, only 51% were completely satisfied, although none were completely dissatisfied with their vagina. The completely satisfied rates for women with CAH who had had surgery and those who had not had surgery were 33% and 40% respectively, with 30% of each of these groups being neither satisfied nor dissatisfied with their vaginas.

Women with vaginal agenesis also belong to the diagnostic grouping of DSD – as their anatomy does not conform to the typical internal anatomy of females. The approach to the management of vaginal agenesis varies in different parts of the world. Dilators are generally used as the first line approach to creating a vagina in the UK (Nadarajah et al. 2005), Australia (Kimberley et al. 2011), and increasingly in the USA (Gargollo et al. 2009). This approach results in a >90% success rate. In some parts of Europe, the use of dilators is limited to the women who already have several centimetres of vagina (usually >4 cm). The alternative approach of using operative techniques, the Davydov (Davydov and Zhvitiashvili 1974), Vecchietti (Borruto 1992), and bowel segment vaginoplasties (Khen-Dunlop et al. 2007) are reported more often from Europe.

Although there has been a small study that demonstrated that the use of dilators did have a negative impact on self-esteem (Liao et al. 2006), the only study to compare women who had had surgical versus dilator therapy to create a vagina had only small numbers of surgical patients (Kimberley et al. 2011), with sexual function in this study similar in both groups. A further predictive factor for sexual function scores was better quality-of-life scores and greater time since diagnosis, underlying the fact that there are a number of factors that contribute to outcome apart from the technique of making a neovagina.

The challenge in the care of young women with vaginal agenesis is the timing of any intervention. In Tubingen, Germany, the decision to undertake surgery (a laparoscopic Vecchietti approach is used), is only made after completion of psychological assessment of the young woman (Sara Brucker, personal communication 2010).

The approach to women with complete androgen insensitivity syndrome (CAIS) also varies – from the use of dilators (Ismail-Pratt et al. 2007), to surgery. It is very hard to separate the negative impact that occurs when the information is given to the young woman that "her vagina is short", and the subsequent reporting that she feels as though her vagina is short. Minto reported that 77% of women with CAIS reported that they felt their vagina was small, yet clinical examination identified this in only 35% (Minto et al. 2003a).

Bladder exstrophy and cloacal exstrophy are now considered part of the DSD spectrum. In these conditions, anomalies of the vagina and uterus are common. In cloacal exstrophy, uterine didelphys is almost routinely present, although these structures may be associated with cervical agenesis and or vaginal agenesis. A high level of

Table 23.3 Reports on the ability to achieve orgasm in women with DSD – with and without genital surgery

	No clitoral surgery	Clitoral surgery
Minto (Minto et al. 2003a) All CAIS	39/59	
Minto (Minto et al. 2003b) DSD with ambiguous genitalia	6/19	7/18
Nordenstrom (Nordenstrom et al. 2010) All CAH	23/24	5/7 amputation 10/10 recession 8/11 reduction
Beerendonk (Beerendonk 2010) mixed DSD population	8/13	11/18

suspicion is essential as the exact internal reproductive tract anatomy has often not been adequately sorted out in the neonatal period when the urinary and bowel anomalies are being corrected. These girls potentially then present at puberty acutely with obstructed systems with haematocolpos and/or haematometra. The young women with bladder exstrophy often have a lower vaginal stricture as a result of the corrective surgery to create a urethra and close the bladder. This will require correction either when they present with vaginal discharge, or when they are ready to use tampons or commence sexual activity.

23.4.4 Genital Sensation and Sexual Function

A further aspect in establishing the long-term impact of genital surgery has been the assessment of sensation. Most of the studies that have been undertaken demonstrate a reduction in sensation following genital surgery (Crouch et al. 2008; Nordenskjold et al. 2008) but the relationship to altered sexual function is not as clear.

Quite a number of reports on sexual function and sexual quality of life in adults with DSD exist, although the quality of these reports varies (Nordenstrom et al. 2010; Warne 2008; Crouch et al. 2008; Schonbucher et al. 2010; Kuhnle et al. 1995). Although the results are inconsistent, overall there is evidence suggesting that the sexual quality of life of individuals with DSD is impaired. The impact of the medical and surgical care, as well as the psychosocial contributions, have not routinely been considered when assessment of sexuality and sexual function has been undertaken.

One approach to try to clarify this is to examine the studies that report on the ability of women to achieve orgasm. When combining the studies that compare women with DSD who have not had external genital surgery to those who have, there is no significant difference in the rate of orgasm ($\text{Chi}^2 = 1.08$, $p = 0.3$) (Table 23.3).

A study on the impact of body image and self-esteem on sexual function has shown that sexual function does not correlate with the severity of a carefully measured genital problem (genital prolapse) but rather with body image and distress scores (Lowenstein et al. 2009).

Ongoing involvement of clinicians, who are comfortable to explore issues relating to sexual function (e.g. sexual counsellors), and with the requisite knowledge regarding the potential problems that may occur as a result of the DSD, is critical.

The potential problems will differ for each of the DSD diagnoses. Women with CAH may require further surgery or the use of dilators to achieve an adequate vagina for intercourse. Women with CAIS will mostly have an adequate vaginal length for intercourse. An exploration of other issues relating to sexual intercourse needs to occur prior to contemplating any surgical intervention, and this includes the exploring the potential negative inputs relating to information given about vaginal length. Women with vaginal agenesis can mostly make their own vagina with the use of dilators, although some will require surgical intervention. Lubrication can be an ongoing issue for those with vaginal agenesis who were born without a hymen, but use of lubrication will assist.

23.5 Gonadal Surgery

For a number of the diagnoses encompassed by the expression DSD, there is no indication for any gonadal surgery. Conditions where there is normal ovarian function such as 46,XX bladder exstrophy, 46,XX cloacal exstrophy and vaginal agenesis, ovarian function is completely normal. For women with CAH, ovarian function is also normal although the negative impact of elevated androgens and potentially obesity may result in irregular menses.

For those conditions where there is an 46,XY karyotype and dysgenetic gonads (e.g., 46, XY complete gonadal dysgenesis, 45,X/46,XY mixed gonadal dysgenesis) the malignancy risk dictates the need for removal of this non-functioning tissue.

In diagnoses such as CAIS, the question of gonadal removal is now openly discussed. For intra-abdominal testes, the risk of malignancy is marginally increased, and monitoring for any change in size with ultrasonography is an option. As these functional testes are producing testosterone which is being converted to oestrogens peripherally, they are serving a useful function. This is particularly the case, if the alternative to performing a gonadectomy may result in difficulties accessing oestrogen replacement therapy, the cost of this replacement medication or where there may be issues with non-compliance. Thus there is a clear argument for leaving the inguinal and labial testes in situ. Their location does carry the potential of pain or discomfort with sexual activity, and removal at that point may then be appropriate after careful discussions.

Gonadectomy for those 46,XY conditions where virilisation has occurred at puberty (PAIS and 17β-HSD3) should be delayed until certainty regarding the gender identity of the young person has been adequately explored. Delay in undertaking the surgery, without any further virilisation can be achieved with suppression of further hormones by the use of gonadotrophin-releasing-hormone agonists.

23.6 Conclusion

The issues encompassed by the gynaecology input overlap with those of other members of the multidisciplinary team involved in the care of the young women with DSD. The exact role undertaken by each clinician is dependent on the clinicians themselves and their specific skills at each centre – but the range of issues that need to be explored are important and require the team to have discussions and good communication to ensure that these issues are covered.

A good understanding of the surgical techniques that may have been used in childhood, as well as having an understanding of surgical techniques that may be required to overcome complications is necessary – and it is probably easiest if the clinician who will be undertaking the corrective surgery is also the one who is talking to the patient about the problems. These problems may not become evident until the young woman is trying to use tampons or is beginning to become sexually active. To clarify what the exact difficulties are requires close co-operation between the surgical members of the DSD team and good communication with counsellors if these clinicians are undertaking the sexual counselling. But most importantly it requires open discussion and communication with the young woman herself.

Timing the initiation of the discussions with the young woman regarding adolescent issues, menses and sexual relationships is challenging. Having the opportunity to "get to know" the young adolescent before this, to establish a trusting relationship, and one that is specifically with the young woman (as distinct to the one with her parents) is part of this process. Gently exploring and tackling these issues before they have a negative impact on the adolescent's development and transition to adulthood is important.

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Psychological Management in Adolescence and Beyond

24

Porpavai Kasiannan

24.1 Introduction

There has been an increase in the interest in the study of infants, children, adolescents and adults with disorders of sex development (DSDs) since the 1990s, mainly stemming from the varied views of medical and psychosocial management of DSDs. It has long been acknowledged that psychological counselling and support should be an integral component of the multidisciplinary standard of care for children with such disorders. The Lawson Wilkins Paediatric Endocrine Society (LWPES) and European Society for Paediatric Endocrinology (ESPE) produced the consensus statement on management of intersex disorders in 2006 (Hughes et al. 2006). The statement recommends that the evaluation and long-term management should be carried out at a centre with an experienced multi-disciplinary team which includes psychology/psychiatry (Hughes et al. 2006). Previously, the Hastings Centre group also recommended that families with children with intersex conditions require multi-disciplinary care (Frader et al. 2004). These recommendations are based on the findings from various follow-up studies that highlight the psychosexual and psychosocial issues that many individuals with DSDs face, as they develop from childhood to adolescents and adults. This chapter will discuss these two aspects in DSDs and their management.

24.2 Psychosocial and Psychosexual Issues in Adolescents and Adults with DSDS

Human development is characterised by dynamic stages which are influenced by internal and external factors from birth to death. Some stages may be characterised by stress and turmoil depending on the individual personality and the available social supports. Adolescence is the major transitional phase from childhood to adulthood creating not only challenges and risks but also opportunities (Kleinemeier et al. 2010). Biological changes in adolescence include brain development leading to increased cognitive development and bodily changes with development of secondary sexual characters. Presence of a chronic physical illness is likely to be more stressful in an adolescent who even otherwise has a number of developmental tasks to negotiate. Psychosocial and psychosexual issues influence one another and do not occur in isolation in general.

At the time of puberty, adolescents with DSDs become aware of the difference in terms of pubertal development compared to peers e.g. amenorrhoea, lack of breast development, atypical appearance of genitalia. This could especially come as a shock in an adolescent who either was not diagnosed or who was not informed of the condition earlier. Atypical appearance of genitals and infertility may be of a lesser importance before puberty but usually becomes a source of concern in adolescents (Cohen-Kettenis and Pfafflin 2003). Delayed or lack of puberty may lead to psychological difficulties at a stage where peer conformity is of prime importance. Cohen-Kettenis and Pfafflin describe low self-esteem and social insecurity because of physical differences, shyness in romantic

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and sexual relationships and fear and insecurity in talking about the condition with a potential partner (Cohen-Kettenis and Pfafflin 2003).

24.3 Psychological Issues in DSDS

There have been only a handful of studies that have looked at the psychological outcomes in DSD. Research has looked at psychological functioning as an outcome of medical interventions and at psychosexual outcomes (gender dysphoria, sexual orientation and gender change) in follow-up studies. Psychological distress has been assessed directly only in some of these studies which have been generally limited by small sample sizes, lack of standardised measures or selection bias (Schutzmann et al. 2009). Slijper et al. report increased risk for emotional problems in children and adolescents (Slijper et al. 1998). Most studies on adolescents focus on physical development especially the hormonal status and its changes during puberty. There are inconsistencies in these studies due to several problems including focusing only on one DSD condition, using different assessment methods, recruiting patients without an accurate diagnosis, and lack of independence of care provider and researcher. Statistics are hampered by small sample sizes and lack of control groups. An observational study conducted by Kleinemeier found no overall psychological impairments in adolescents with DSD, but found special needs in the group warranting support with shame, stigmatization and coping with normative pressures. The diagnostic groups that were under-represented in their study were the girls with no androgen effect and boys with DSD, the possible reasons being the girls being uninformed of their condition and denial associated with boys (Kleinemeier et al. 2010).

One long-term follow-up study of female patients with congenital adrenal hyperplasia (CAH) found them to have negative body image and anxiety associated with sexuality (Kleinemeier et al. 2010). Studies of adolescents with CAH and uro-genital abnormalities have not consistently found psychological impairment. In one study, female adolescents and adults with CAH were found to have higher scores on aggression scales compared to siblings and cousins. These findings are suggestive of prenatal androgen exposure which is stronger in the seriously affected salt-wasting type than in the simple virilising type (Cohen-Kettenis and Pfafflin 2003).

Individuals with Turner Syndrome have impaired visuo-spatial, motor, verbal fluency, short term memory and executive function performance. They also have social difficulties, deficits in social cognition, face recognition and identification of facial expressions of emotion and some may be at increased risk of autism spectrum disorder (Hines 2004). Individuals with Klinefelter syndrome have a higher risk of having learning and behavioural difficulties, are often shy, passive, quiet, immature and dependant and less masculine. During adolescence and transition through puberty, boys who had Klinefelter syndrome showed low self-esteem, anger, frustration or depression. Boys with 47, XYY have somewhat lower IQs although in the normal range, some language and speech deficits and increased motor activity and distractibility. Studies in the 1960s and 1970s indicated increased risk of criminality in this group which was not always replicated in subsequent studies. Studies in the late 1990s report higher incidence of antisocial behaviour and more criminal convictions than controls (Cohen-Kettenis and Pfafflin 2003).

Few adult follow-up studies have been conducted on DSD populations. In Diamond and Watson's study population, 24 (62%) of those who had CAIS had considered suicide and 9 (23%) had attempted it. Among those who had PAIS, 11 (61%) had considered suicide and 3 (17%) had attempted it. The three who had attempted suicide did so before switching from their sex of rearing. Frequently, these considerations and attempts were associated with learning of their diagnosis or a problem with a specific amorous relationship (Diamond and Watson 2004). Another adult study by Warne et al. which fulfilled methodologically high standards on a group of heterogeneous adults found that the rates of psychological distress were similar to samples of persons with chronic somatic diseases. The group with DSD reported lower self-esteem, higher trait anxiety, higher extraversion and more interpersonal problems than one of the comparison groups (Warne et al. 2005). Schutzmann et al. conducted a pilot study on a diverse group of 37 adults with DSD using the Brief Symptom Inventory to assess self-reported psychological distress. Their results suggested that adults with DSD were markedly psychologically distressed with rates of suicidal tendencies and self-harming behaviour on a level comparable to non-DSD women with a history of physical or sexual abuse, but concluded that their sample recruitment procedures did not permit a firm generalization (Schutzmann et al. 2009).

According to Karkazis, there is a belief that if the child was not anatomically correct, this might lead to increased risk of suicide later in life. She reports that several adults that she interviewed have considered suicide and whose desperation did not result from diagnosis per se, but from how their family, physicians and society had perceived and treated them throughout their lives (Karkazis 2008). This can only be confirmed by long-term studies comparing individuals who have been treated surgically and not. There are other losses that may result in the form of relationship breakdowns due to partner's lack of understanding of the distress of an individual with a DSD or may be due to sexual incompatibilities.

An area which is worth considering is the long-term effects of surgery in infancy. Psychosocial adjustment is a complex phenomenon and is influenced by multifaceted inter- relationship between the child and family factors. Ludman summarises in her review that the period between 6 and 48 months as the most vulnerable developmental stage for developing adverse effects of hospitalisation. She reviewed studies exploring long-term effects of major paediatric surgery in congenital anomalies of the alimentary tract and concluded 'despite inconsistencies, the evidence suggests that, irrespective of the presence of chronic health problems, children who require major paediatric surgery are at a two to three times greater risk for psychiatric disorder than healthy children' (Ludman 2006). This is an area that needs further attention in relation to the long-term effects of early surgery for DSDs as there are no methodologically sound studies that have evaluated this issue.

24.3.1 Sports and DSDs

DSDs came into public view when Caster Semenya, a South African athlete, won the 800 m sprint in the world championships in Berlin in 2009. As questions were raised by fellow athletes, The International Association of Athletes Federation (IAAF) required Semenya to undergo a full physical evaluation and gender verification testing including reports from a gynaecologist, an endocrinologist, a psychologist, a gender specialist and an internal medicine specialist. Subsequently after a prolonged wait, Semenya was allowed to retain her title and was allowed to participate in sports. The results of the testing were not released for privacy reasons (O'Reilly 2010). There were a number of discussions in the media regarding gender, DSDs and sports following this incident. This was not the first time DSDs have taken centre stage in sports. There have been other reports of such incidents dating back to the 1930s.

Gender verification was mandatory until the 1996 Olympic Games in Atlanta at which out of 3,000 tests administered, eight showed up positive. Upon further examination, seven of those athletes were found to have AIS and the eight had an enzyme deficiency. All eight athletes were given the go-ahead to compete (O'Reilly 2010). Since discontinuing mandatory gender verification, the IOC has championed case-by-case evaluation of athletes with suspected gender disorders (Handley 2010). Following the Semenya case, a symposium of experts was held at Miami in January 2010 by the International Olympic Committee (IOC). Among the symposium's conclusions were recommendations that medical centres of excellence specialising in DSD be set-up around the world, that athletes have periodic pre-participation health exams, that athletes with a gender ambiguity be diagnosed and recommended treatment as quickly as possible and that rules of eligibility for competition for such athletes be established (Handley 2010; O'Reilly 2010).

The most recent IOC recommendations, as defined by a group of experts, are as follows: (1) A female recognised in law should be eligible to compete in female competitions provided that she has androgen levels below the male range (as shown by the serum concentration of testosterone) or, if within the male range, she has an androgen resistance such that she derives no competitive advantage from such levels. (2) An evaluation with respect to eligibility should be made on an anonymous basis by a panel of independent international experts in the field of hyperandrogenism that would in each case issue a recommendation on eligibility for the sport concerned. In each case, the sport would decide on an athlete's eligibility taking into consideration the panel's recommendation. Should an athlete be considered ineligible to compete, she would be notified of the reasons why, and informed of the conditions she would be required to meet should she wish to become eligible again. (3) If an athlete fails or refuses to comply with any aspect of the eligibility determination process, while that is her right as an individual, she will not be eligible to participate as a competitor in the chosen sport. (4) The investigation of a particular case should be conducted under strict confidentiality (IOC 2011).

There a number of issues that makes the IOC's view on DSDs quite controversial. Many athletes who agree to gender testing may find it shocking and painful to discover their intimate problem revealed by sports officials. Variation in hormone levels even in typical females makes understanding baseline levels difficult. Robert Ritchie reports that there is no evidence that female athletes with DSD display sports-related physical attributes which have not been seen in biologically normal female athletes (Ritchie et al. 2008). Ambiguity in gender can take many forms and can range from mild to pronounced. It is difficult to find the cut-off point where gender ambiguity becomes a genetic advantage and an unfair sporting advantage.

Sport is not the only arena where individuals with a DSD face issues. Other institutions, especially the armed forces, are another area where adults with DSD may face problems. Empirical research in this area is lacking. There is a general assumption that Western countries are more advanced than other nations regarding gender and sexuality. However, recognition of intersex and trans-sexual people is still rare in military and other higher offices even in the west.

24.4 Psychosexual Issues in DSDs

24.4.1 Psychosexual Development

Psychosexual development is a species-centred conception of human development that encompasses sexual differentiation, sexual development, sexual behaviour, gender-typical social affiliation, pairing, reproduction and parental care. The concept of gender identity encompasses cognitive (understanding of being a boy or a girl) and affective (feelings of contentment with one's gender) components. The term gender identity is used to denote a person's sense of themselves being male, female or indeterminate. Gender role refers to behaviours, attitudes and personality traits that a society, in a given culture and historical period, designates as male or female social role (Cohen-Kettenis 2010). In adolescents and adults, gender role is measured using stereotypic masculine or feminine personality attributes or with regards to recreational and occupational interests and aspirations (Cohen-Kettenis 2010).

Psychosexual development is traditionally conceptualised as three components. Gender identity refers to a person's self representation as male or female (with the caveat that some individuals may not identify exclusively with either). Gender role (sex-typical behaviours) describes the psychological characteristics that are sexually dimorphic within the general population, such as toy preferences, play and playmate preferences and physical aggression. Sexual orientation refers to the direction(s) of erotic interest (heterosexual, bisexual, homosexual) and includes behaviour, fantasies and attractions. Psychosexual development is influenced by multiple factors such as exposure to androgens, sex chromosome genes and brain structure, as well as social circumstances and family dynamics.

Theories have varied over the years regarding psychosexual development in children and adolescents. John Money reasoned that sex of rearing, if assigned early enough in childhood and if appropriately matched with external genitalia, is the most important determinant of gender identity. This theory dominated the rationale behind management of children with DSDs during a major part of the 1990s (Karkazis 2008). Such neonatal interventions although not affecting the children early on do have implications for the adolescent and adult. Studies that followed did not support the concept that form and function and the appropriate environment alone were sufficient to determine future gender identity and gender role.

Gender identity is affected by neurobiological processes that interact with general and specific environmental influences (Reiner 2004). There are not many systematic studies that look at the typical psychosexual development in children. The focus on atypical gender behaviours in children ignores the broader and richer dimensions of human sexuality. Meyer-Bahlburg's review found very marked variations between syndromes in the prevalence of patients who are not satisfied with their assigned gender and undergo gender change. He found gender change from female to male more frequent than from male to female and that gender identity problems were not prevalent even in female-raised patients with a history of normal-male prenatal androgen exposure, and if they do develop, it may not occur before adolescence or even adulthood (Meyer-Bahlburg 2005). He concluded that there was no evidence to support a perspective of a specific biological factor overriding all others and determining gender identity.

24.4.2 Gender Dysphoria/Gender Identity Disorder

Gender dysphoria denotes dissatisfaction with one's assigned gender. There is considerable evidence that individuals with a DSD experience gender incongruence or gender dysphoria and may wish to change from their assigned gender which is also known as Gender Identity Disorder (GID). From a phenomenologic perspective, DSD individuals with gender dysphoria have both similarities and differences to individuals with gender dysphoria with no known DSD. Developmental trajectories also have similarities and differences. The presence of a DSD is suggestive of a specific causal mechanism that may not be present in individuals without a diagnosable DSD. Gender dysphoria appears more frequently in the DSD population compared to general population, but it has been difficult to predict from karyotype, genital virilisation, prenatal androgen exposure and assigned gender (Cohen-Kettenis 2005; Zucker 1999). The context in which gender problems occur in intersex persons is sufficiently different from the non-intersex situation. However regarding GID in non-DSD individuals, there is currently much speculation about genetic and/or hormonal, brain-specific mechanisms that underlie neuro-anatomic changes and, thereby, induce a form of intersexuality that is limited to the central nervous system (Meyer-Bahlburg 2005).

24.4.3 Diagnosing Gender Identity Disorder/Gender Dysphoria

The current Diagnostic and Statistical Manual (DSM-IV-TR) of the American Psychiatric Association (2005) categorizes individuals with intersexuality (DSD) and related conditions who experience gender identity problems as Gender Identity Disorder Not Otherwise Specified (GID-NOS). It reserves the unqualified GID diagnosis for non-intersex patients with sufficiently severe gender problems as manifested by a strong and persistent cross-gender identification and persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex (APA 2005). The DSM is currently undergoing revision with DSMV expected to be finalised by end of 2012. The International classification of Diseases (ICD) has different criteria for Gender Identity Disorders in boys and girls and recommends the use of either Other Gender Identity Disorders or Gender Identity Disorder Unspecified category for those with intersexed conditions (WHO 1992).

Proposed DSM V Criteria for Gender Incongruence (GI) in Adolescents or Adults requires a marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by two or more indicators from six indicators of gender dysphoria. The indicators are a marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or, in young adolescents, the anticipated secondary sex characteristics), a strong desire to be rid of one's primary and/or secondary sex characteristics(or, in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics), a strong desire for the primary and/or secondary sex characteristics of the other gender, a strong desire to be of the other gender (or some alternative gender different from one's assigned gender), a strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender) and a strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender). The proposed subtypes of gender incongruence include GIs with a disorder of sex development and without a disorder of sex development (APA 2010).

The central aspect of medical decision-making early in life in DSDs is assignment of gender early in life. This has led to increasing research into the different aspects of psychosexual development including assessment of gender identity, gender role and sexual orientation later in life. Various measurement tools are available to assess the psychosexual differentiation of individuals born with DSDs (Zucker 2005). The main assumptions in the designing of these instruments were that the measures should be related to empirical evidence for normative gender differences, that some human behavioural sex differences have a parallel in non-human primates and that they should be consistent with or related to cultural definitions of masculinity and femininity (Zucker 2005). This again is based on the prevailing binary view of the world regarding gender differences.

There are around 20 measures available for measuring gender identity in young children with equally distributed parents and child measures. Zucker discusses 11 measures to assess gender identity and 4 measures to assess sexual orientation. Most adolescent and adult assessments rely heavily on the DSMIV criteria for Gender Identity Disorders (APA 2005). Measuring gender in a dichotomous fashion in adolescents and adults does not provide rich information a dimensional approach might provide. However, the psychometrics of such measures have not been studied in depth (Zucker 2005).

Zucker's Gender identity questionnaire in adults attempts to measure gender identity and dysphoria in a dimensional manner and appears promising in studying adults with DSDs.

24.4.4 Psychosexual Outcomes

24.4.4.1 Congenital Adrenal Hyperplasia (CAH)

Prenatal androgen exposure is associated with certain aspects of psychosexual development e.g. cross-gender toy and play and playmate preference in CAH girls with severe mutation and marked genital virilisation. Other psychological characteristics like sexual orientation and maternal interest are also influenced by prenatal androgen exposure (Hughes et al. 2006). Some studies have reported male-typical behaviours and attributes, but not gender identity, in genetic females who were exposed to prenatal androgens from congenital adrenal hyperplasia. Several studies of girls with CAH from several different cultural settings also suggest that levels of androgen exposure early in development influence sex-typed play behaviour (Hines 2004). Hines notes that despite prenatal androgen exposure, virilised genitalia at birth and male-typical play behaviour girls with CAH assigned and raised as girls develop a female gender identity (Hines 2004). Dessens et al. reviewed the literature on gender identity, gender dysphoria and gender change in chromosomal females with CAH raised male or female. They found that 94.8% of patients raised as female later developed gender identity as female, but 5.2% had serious problems with gender identity. Among patients raised as male, serious gender identity problems were reported in 12.1% of patients (Dessens et al. 2005). Another review by De Vries et al. found that 10 of 217 (5%) of adolescents raised as female and adult women with CAH had some form of gender dysphoria (De Vries 2007). There is also some evidence that genetic girls with CAH reared as males can be content as men (Hines 2004). Hines in her review concluded that there was substantial evidence to associate CAH with reduced heterosexual orientation, reduced satisfaction with female sex of assignment and some evidence of increased tendency to physical aggression and reduced interest in infants and childcare. The majority of women with CAH are heterosexual, but the incidence of homosexuality compared to population norms is increased. Delayed psychosexual milestones, low interest in maternal role, lower than normal fertility and low sexual motivation are other findings (Cohen-Kettenis and Pfafflin 2003).

24.4.4.2 Complete Androgen Insensitivity Syndrome (CAIS)

In CAIS childhood gender role behaviour, gender identity and sexual orientation in adulthood are the same as in other females which highlights the importance of sex hormones rather than sex chromosomes for psychological sex differentiation (De Vries et al. 2007; Hines 2004).Mazur reviewed all articles on CAIS, PAIS and micropenis published until 2004 and concluded that only 9.1% of individuals with PAIS changed gender and that gender dysphoria appeared to be a rare occurrence (Mazur 2005). This review acknowledged a number of limitations in the studies reviewed including varying degree of accuracy in diagnoses, small sample sizes, lack of accurate descriptions of neonate's genitalia, sample from support groups, incomplete follow up, lack of independent assessment of gender issues and lack of quality assessment methods. Due to these limitations, the results are unlikely to provide an accurate measure of gender identity outcome.

24.4.4.3 Partial Androgen Insensitivity Syndrome (PAIS)

Among patients with PAIS, androgen biosynthetic defects, and incomplete gonadal dysgenesis, there is dissatisfaction with the sex of rearing in about 25% of individuals, whether raised male or female. In the review by De Vries et al. (2007), 46 PAIS adolescent and adult individuals raised female, 5 (11%) were gender dysphoric or changed gender and 5 among the 35 PAIS group raised male were gender dysphoric or changed gender (De Vries et al. 2007). Available data support male rearing in all patients with micropenis, taking into account equal satisfaction with assigned gender in those raised male or female, but no need for surgery, and the potential for fertility in patients reared male (Hughes et al. 2006).

24.4.4.4 Enzyme Deficiencies

In 1979, Imperato-McGinley reported that genetic males with 5-alpha-reductase deficiency (5α-RD) raised as females transitioned to male during puberty. Cohen-Kettenis reviewed studies on gender change in XY individuals more than 12 years of age raised as female who had 5α-RD or 17β-hydroxysteroid dehydrogenase deficiency (17β-HSD3), previously known as 17-ketosteroid reductase deficiency (17-KRD). Gender role changes were reported in 56–63% of cases with 5α-RD and 39–64% of cases with 17β-HSD who were raised as girls. The changes were usually made in adolescence and early adulthood. In these two syndromes, the degree of external genital masculinisation at birth does not seem to be related to gender role changes in a systematic way. Cohen-Kettenis summarised that a masculine appearance in childhood, in association with masculine behaviour (perhaps both partially caused by prenatal exposure to androgens), make a gender role change likely after the pubertal changes as they reinforce an already existing gender discomfort (Cohen-Kettenis 2005). Sobel and Imperato-McGinley in their review of XY DSD looked at the histories of individuals who have 5α-RD deficiency and 17β-HSD and concluded that gender identity was not merely a function of parental and societal influence. Even if raised as girls, these individuals were biologically driven to be male as a natural course of events (Sobel and Imperato-McGinley 2004), although this may not have been the case if the testes had been removed in early infancy. This is still an unresolved issue.

24.4.4.5 Other DSDs

Psychosexual development and sexual orientation have not been studied in depth in some DSDs, such as Turner syndrome. They have female gender identity with feminine interests and activities. One study suggested that they are more likely to show an undifferentiated psychosexual profile compared to other females (Hines 2004).

Individuals with Klinefelter syndrome reported less sexual interest in girls and had a significantly later onset of masturbation (Diamond and Watson 2004). Gender expression in Klinefelter syndrome ranges from androgynous or feminine feelings to considering themselves as transgendered, intersex or trans-sexual (Diamond and Watson 2004). Despite such features, a large majority have masculine gender identities (Cohen-Kettenis and Pfafflin 2003). In males with 47, XYY DSD, gender identity was not a problem in general, other than a few reports of gender identity problems and even trans-sexualism (Cohen-Kettenis and Pfafflin 2003). Grumbach's group noted that genetic males who had micropenis fared tolerably well even when reared female. Reiner found that males who were born with cloacal exstrophy, whether raised as male or castrated at birth and raised as female, demonstrate psychosocially and psychosexually dominant male-typical tendencies. He also noticed the ease of transition in many of the boys some of whom did not know their birth history. He concludes that prenatal androgen exposure and perhaps sex chromosome-specific neuronal properties influences gender role, and, at least sometimes, creates male sexual identity, even if males are castrated at birth and reared female (Reiner 2004). Less systematic studies have been done in other rare DSDs such as congenital penile agenesis, ovotesticular DSD, mixed gonadal dysgenesis, Leydig cell hypoplasia and vanishing testis syndrome, all of which are associated with genital malformation and ambiguity.

24.5 Psychological Management in Adolescents and Adults

Treatment of individuals with DSDs involves the input of various disciplines. Although DSDs are primarily medical conditions requiring medical and surgical management, they have significant impact on the individual's psychosocial and psychosexual life as discussed above. They also impact the family and social life to varying degrees. The consensus guidelines acknowledge the significance of psychosocial care and the involvement of mental health staff with expertise in DSD. The importance of a psychologist, psychiatrist or similar professional, in the management of DSD is not about pathologising DSD, but rather is about the recognition of the exceptional personal and social issues a diagnosis of DSD presents (Brain et al. 2010). Psychological interventions vary between diagnoses and should be tailored to meet the individual needs including regular monitoring and ethical approval of challenges that each treatment and regular validation of informed consent. According to Reiner, a child psychiatrist is an ideal candidate to be the 'point player' on the treatment team (Reiner 2004).

The important roles of the psychologist, psychiatrist or other mental health professional in DSD care are assessment and management of gender identity issues, information management including facilitating team decisions, addressing psychological aspects of surgery and management of issues of sexuality (Brain et al. 2010; Cohen-Kettenis 2010; Hughes et al. 2006). In adolescence, the individual may encounter learning and social problems, physical discrepancies compared to peers, precocious or delayed puberty, surgery, medication including hormones, nonsurgical genital treatment e.g. vaginal dilators, and technical aids for sexual contact, infertility and sex reassignment. Individuals adapt and integrate aspects of their condition depending on the emotional and cognitive maturity, the amount of information received and the existing family and social support. Many of them, especially the ones with chromosomal abnormalities, may require speech and language therapy, assistance with learning, occupational therapy and medication for behaviour problems. All individuals diagnosed with DSD should be offered appropriate psychological assessment, emotional support, counselling and sometimes psychotherapy to enable them to lead a meaningful life despite vulnerabilities.

24.5.1 Initial Diagnosis in Adolescents and Adults

Most causes of DSD are recognised in the neonatal period; later presentations in older children and young adults include: previously unrecognised genital ambiguity; inguinal hernia in a girl; delayed or incomplete puberty; virilisation in a girl; primary amenorrhoea; breast development in a boy; and gross and occasionally cyclical haematuria in a boy. Unless the family knows they carry X-linked CAIS, it is usually not diagnosed until abdominal testes herniate or menarche fails to occur. This can come as a huge shock to an adolescent who may react with feelings of rage and grief. They need appropriate support and treatment focused on their feelings around body image, enhancing social skills and self-esteem and improving coping skills. They also will need help in coming to terms with the fact that their bodies will not change. Adolescents with DSDs need appropriate psychosexual education tailored to their individual needs.

Rarely, the diagnosis of DSD comes as a surprise in adulthood. The first presentation may be to a psychologist or psychiatrist with gender dysphoria, or more rarely due to gender verification tests done in athletes by sporting authorities. They require a thorough history and physical examination, karyotyping, consideration of the degree of brain masculinisation and psychiatric assessment. A thorough psychiatric assessment bearing all the dimensions of the bio-psycho-social model is warranted to make sense of the patient's gender, sexuality and general psychological well-being (Bostwick and Martin 2007). Potential psychiatric differential diagnoses include psychosis, somatic or religious delusions, body dysmorphic disorder, neurotic conflicts about sexual orientation and borderline or schizotypal personality disorders (Bostwick and Martin 2007).

24.5.2 Information Management

Information management in the DSD context involves disclosure of information both from clinicians to parents and child and from child and family to the wider environment (Cohen-Kettenis 2010). The issues that are raised in adolescence include hormone replacement, need for regular medical follow-up, decisions about surgical interventions and issues around gender identity and sexuality. Discussing these issues may raise other difficult emotional issues. Issues around gender role behaviours and sexuality may give rise to significant anxiety if the condition is not fully understood especially in the context of less than optimal cognitive processing due to the emotional load. This warrants repeated explanations tailored to the individual's developmental stage.

Being well informed about one's medical condition is associated with better psychological adjustment. Studies done in children with HIV suggest that children who know their HIV status have higher self-esteem than children who are unaware of their status. Parents who had disclosed the HIV status to their children experienced less depression than those who did not (COP 1999). Disclosures made to children and adolescents should take into account not only their age but also the level of cognitive functioning, psychosocial maturity and the complexity of family dynamics. The mental health professional should be well-informed in developmental issues and the impact of chronic illness on emotional well-being. As DSDs have varied aetiology, presentation and long-term outcomes, information provided will need to be appropriate to the clinical context.

Young children with DSD would benefit from simple information regarding the nature of illness and about what they need to do to care for themselves. As children mature, they need to be fully informed about their condition and encouraged to actively participate in the treatment process. Appropriate resources in the form of children's books can be useful, a list of which are currently available in some support-group websites (AISSG 2011). However, in the case of DSDs, some parents may be reluctant to disclose to their children due to fear, shame or to prevent negative emotional consequences. Parents also are likely to fear discrimination, stigmatisation or ostracism from other children and families. Such parents will need a lot of support and reassurance before information is disclosed to the children. Appropriate resources for parents should be provided whenever possible in the from of booklets, support groups and websites. Values regarding sexuality and gender vary between cultures which can be another impediment to adequate disclosure. Despite the current trend in ethical practice being based on honesty and full disclosure some physicians especially in some cultures may still be reluctant to disclose fully to the child or adolescent. Disclosure is also paramount in obtaining informed consent for medical and surgical interventions in adolescents by enabling them to become well-informed participants in important health care decisions. When individuals reach adulthood they need to know the whole truth about their condition, including the karyotype. This is one area which creates a lot of discomfort for parents and clinicians. Information should be provided in a sensitive and thoughtful manner focusing on the strengths of the individual with no ambiguity in the language used. Accurate written information in simple language should be provided at all stages of information provision. This gives the individual and the family opportunity to review the information in their own environment and to raise questions with the professional in the follow-up visits (see also chapter 12.8).

Families may also seek advice regarding disclosure to the wider social environment. Some parents may be reluctant to fully inform their children due to anxiety that the child might share the information with others and may become a target for bullying and ridicule. There are no clear guidelines regarding the consequences of sharing information with the wider environment. Clinicians generally base their advice on their own personal perspectives and intuition taking into account the individual family and social circumstances. Various aspects of this process need further study to improve clinician's insight into how they time and share information with patients and families. Studies comparing the development of children living in 'informed' versus 'uninformed' environments would be valuable (Cohen-Kettenis 2010).

Another area that requires appropriate disclosure is regarding potential gender identity issues in future. Evidence from the existing literature reveals that knowledge regarding predictability of gender identity problems in certain DSDs is limited. It is important that patients and parents are informed of this and appropriate psychological help offered to help understand the specific nature of problems. When full disclosure had been an issue, gaps in knowledge may persist into adolescence and adulthood. This can create a number of difficulties in the interpersonal relationships within the family system in adolescence. Even when there has been full disclosure, it is likely that some irreversible decisions have already been made which can make the adolescent very angry. However, this situation is likely to be better resolved by further discussions compared to a situation where the adolescent was not aware of their condition.

Child psychiatrists may be called to assess decisional capacity in complex cases for clinical decision-making and for legal requirements. In Australia, gonadectomy and pubertal suppression decisions are made by the Family Court where a child psychiatrist may be called upon to assess the adolescent's ability to understand the treatment options. Assessment of decisional capacity has three standard elements: (1) The ability to understand the nature of the medical problem; (2) The ability to appreciate the alternative medical responses to it (including the option of no treatment and the advantages and disadvantages of each option); and (3) The ability to express a choice. It is common to add a fourth element: The ability to apply reasonably stable personal values to the process of arriving at a considered preference (Kipnis 2004).

The nurturing of decisional capacity may be an important and realizable clinical goal in the multidisciplinary DSD team. Health care professionals need to assess decisional capacity in the individual patient and look for evidence of capacity in those who are between the ages of 7 and 14 and for evidence of incapacity in those who are older than 14. A good framework to adopt would be that of Kipnis': 'the work of the child and adolescent psychiatrist has to take into account the minor patient's present and future needs and interests and his/her emerging decisional capacity, the parents' responsibilities and aspirations for the child, and the state's interests in promoting sound child-rearing and protecting children from abuse and neglect' (Kipnis 2004).

24.5.3 Medical Trauma

A number of aspects of treatment which include regular medication, frequent medical reviews including blood tests and surgery or other procedures are similar to a chronic illness. These experiences can be stressful for both parents and the children. Many parents are also concerned about the general physical well-being of their children particularly in conditions like salt-wasting CAH. It is not common these days for children or adolescents to be examined in grand rounds or educational sessions. However, their medical reviews may still involve full body examinations, genital exams and sometimes photographs and discussion with parents in the presence of the child or adolescent. Such experiences may be quite traumatic for some. This kind of trauma can be avoided by restricting the genital exams to only when absolutely necessary and when necessary by taking time to explain the need for exams and photographs and by obtaining adequate informed consent. Follow-up treatment and medication can sometimes have side effects and cause a lot of pain. This is an important issue in adolescents who have vaginal surgery and may need dilation of the new vagina to prevent scarring.

Some parents interviewed by Karkazis reported grieving not only for the loss of the son they thought they had but also for their imagined life in which they had pictured a perfect baby with no health concerns. Their concerns also extend in the longer term into fears that their child may have been assigned the wrong gender, anxieties about how the child will survive all the typical experiences of childhood, puberty and adulthood (Karkazis 2008).

24.5.4 Puberty and Sexuality

Puberty can prove very difficult for individuals with a DSD. This is generally the time when they consolidate their understanding of what having a DSD means in relation to their bodily and sexual development. For some, it may be the first time they learn about their DSD status. Sexuality and forming intimate relationships are important tasks of adolescence. Adolescents with DSD may have a number of anxieties in entering this phase especially if they have history of early medical trauma in the form of repeated genital examinations, medical photography or differential treatment by clinicians. In general, sexual problems appear to occur more in DSD compared to non-DSD individuals. Some adolescents with DSD feel uncertain about sexual adequacy, sexual orientation or gender identity when they enter puberty. They may delay initiating intimate relationships due to their insecurities. Due to the nature of these difficulties, adolescents need adequate and timely medical and sexual education and also have the opportunity to discuss their concerns in private with a mental health clinician (Cohen-Kettenis 2010). Around puberty, adolescents will need preparation for hormone therapy. They need accurate information regarding the need for hormones, forthcoming bodily changes, sexual thoughts and feelings. Sometimes adolescents may rebel against their parents or their situation by non-compliance with treatment. They may need additional professional support at such crucial developmental stages. If vaginal dilation is required, success rates are good but are directly related to compliance. Support from a psychologist and supervision from a dedicated clinical nurse specialist are important. This usually provides an opportunity to explore worries about current and potential sexual relationships (Brain et al. 2010).

24.5.5 Gender Assignment and Reassignment

Decisions on gender assignment can only be made after careful consideration of medical and psychosocial pros and cons and usually depend on the predicated optimal outcome. Unfortunately, adult gender identity cannot always be accurately predicted in some conditions. Gender assignment decision-making relies not only on the surgical possibilities, potential for fertility and need for hormone replacement but also on the potential for psychological and psychosexual functioning as male or female and the ability of parents to cope with uncertainties and complexities related to decision making (Cohen-Kettenis 2010; Hughes et al. 2006). Sometimes a correct diagnosis is only made after the child has been assigned to one gender, but the diagnosis may indicate appropriateness of assignment to the opposite gender. Moreover, in children with DSD, the process of gender development is likely to be different. The issue gets even more complex in an adolescent newly diagnosed with DSD. A degree of consensus exists for gender assignment for some diagnoses. In CAIS and CAH with moderate virilisation, the gender assignment as female is not disputed. However, there are no clear guidelines for other diagnoses like 5-alpha reductase deficiency and PAIS, to name a couple.

It is clear from a number of follow-up studies discussed earlier that the gender role behaviour may be inconsistent with assigned gender. This may be misconstrued as gender dysphoria by parents who may feel guilty for wrong decision making. This anxiety can be avoided by regular follow-up by the treating team. Despite careful multidisciplinary assessment prior to gender assignment in DSD and regular reviews, there will be the occasional adolescent or adult who would later present with significant gender dysphoria.

In cases of persistent gender dysphoria, the individual should be assessed by clinicians skilled in the assessment and management of gender dysphoria and gender change. The standards of care of the World Professional Association for Transgender Health (WPATH, a professional organisation in the field of gender dysphoria) are helpful in the assessment and management of persistent dysphoria in individuals with DSD (Meyer et al. 2001). A thorough understanding of the gender variant behaviour against the broad background of functioning of the child and family is necessary. A number of instruments that are available to aid the assessment in gender variant individuals are also useful in the cases of gender dysphoric children with DSD (Zucker 2005).

Standards of Care of the WPATH outline stages of gender reassignment. The initial phase is the diagnostic phase to establish DSM or ICD diagnosis of Gender Identity Disorder. The next phase consists of real-life experience (RLE) in the desired role, hormones of the desired gender and surgery to change genitals and other sex-related characters (Meyer et al. 2001). In adolescents, puberty-delaying hormones are generally initiated after Tanner stage 2 or 3. In contrast to gender dysphoric adolescents without DSD, agonadal adolescents with DSD do not need suppression of puberty. However, they may benefit from delaying hormone replacement therapy which is likely to give them more time to reflect on their wish to change gender and to prepare psychologically and practically for gender change (Cohen-Kettenis 2010). Gender reassignment surgery is only carried out in adulthood and may be more complicated in individuals with DSD due to the effect of previous genital surgeries.

24.5.6 Infertility

Infertility is a common consequence of DSDs. Even in individuals where infertility is not as a result of gonadal failure, it may still be an issue due to anatomical problems warranting intervention. Literature available on the issue of infertility in individuals with DSD is limited to personal accounts in interviews. According to the World Health Organisation (WHO), infertility affects up to 15% of reproductive-aged couples. Although male infertility is the cause in 50% of cases, the social burden falls disproportionately on women. In many cultures, childless women suffer discrimination, stigma and ostracism (WHO 2010). Advances in treatment of infertility and in preservation of sperm or ova for the future have increased the possibility of fertility options in some individuals with DSDs. In many, infertility is untreatable. This in turn has a number of psychological implications which need addressing from a young age especially in adolescence so that they can make informed decisions about fertility choices. In rare cases where the diagnosis of DSD is made while being investigated for infertility, the psychological issues can be even more complex.

24.5.7 Role of Support Groups

The value of peer and parent support for many chronic medical conditions is widely accepted, and DSDs, being lifelong conditions which affect developmental tasks at many stages of life, are no exception. A number of support groups and organisations are available in different countries usually based on a particular condition like CAH or AIS. Support groups offer a safe place where individuals and families feel accepted without isolation or stigma and where very private concerns can be discussed with others who have experienced similar issues in life.

While clinicians are focused on gender and genital appearance as key outcomes, support groups' focus is on stigma and experiences associated with having a DSD.

Support groups complement the work of the health care team and, together, can help improve services and quality of life for individuals with DSDs. Initiatives by support groups have led to improvements in management of DSD and research directed towards clinically relevant issues. Dialogue between health care professionals and support groups, and collaboration as partners is to be encouraged (Hughes et al. 2006).

24.6 Future Research Focus

The available data on the psychological and psychosexual outcomes of DSDs is neither systematic nor comprehensive. Future follow-up studies on individuals should focus not only on the medical and surgical outcomes but should appropriately focus on psychological functioning, quality of life and psychosexual functioning and their outcomes. Research should also aim at developing measures and toolkits for identifying families that are at risk and make them accessible (Cohen-Kettenis 2010). More rigorous research should be undertaken to formulate appropriate clinical guidelines for psychological assessment and management of the various types of DSDs and gender dysphoria in individuals with DSDs.

Studies should also be aimed at investigating the various aspects of information management including the timing, type and method of conveying information that is culturally sensitive. These then would lead to the development of evidence-based information management protocols. Evidence-based information/educational material regarding the various DSD conditions, their medical and psychological management should be developed for children, adolescents, families and professionals.

Although there is consensus regarding gender assignment at infancy in some DSD conditions, there is no sound empirical basis in others. Gender assignment at birth so as to avoid future gender dysphoria or gender reassignment is one of the highly controversial issues in this field. DSDs are quite diverse and rare which makes studying them systematically difficult. International collaborative efforts similar to the Euro-DSD project based at Cambridge University are necessary for systematic long-term follow-up. Long-term follow-up comparing psychosocial and psychosexual outcomes in individuals who had surgery as infants with those who did not is likely to help resolve the debate for and against surgery.

24.7 Summary

DSDs affect not only anatomical and physiological development of the individual but also their thoughts, feelings, sense of self and relationships with immediate family and the extended social network. It is therefore paramount that DSD management always needs a multidisciplinary approach with a mental health professional with expertise in DSD being an integral part of the team. Psychological support to the patient and the family should be an integral part of the treatment programme irrespective of age or the clinical condition. Psychological management should focus on providing accurate non-confusing information and preparing young adolescents to face the issues in life in general and sexual life in particular due to the consequences of the DSD and its treatment. Specific psychological interventions vary between different diagnoses and will need to be tailored to meet the individual needs including regular monitoring of general psychological well being, assessment of gender identity where appropriate and regular validation of informed consent. Whilst certain aspects of the management of DSD clearly require input from a psychiatrist or psychologist, their actual role in the multidisciplinary team evolves with the team and it is this dynamic integration of medical and psychological support that provides the best model of care. Understanding the psychological and psychosexual outcomes in individuals with DSD is a continuously evolving field. Not only the emerging evidence, but also the individual's lived experience, the family's predicament and the prevailing social construct need to be considered in depth when trying to formulate the best psychological care. It is important to acknowledge that despite all the odds a number of individuals with DSD are highly resilient, true to the words of Helen Keller 'Although the world is full of suffering, it is also full of overcoming it'.

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Short-, Medium- and Long-Term Outcomes Following Surgery for Disorders of Sex Development (DSD) at Royal Children's Hospital

25

John M. Hutson, Garry L. Warne, and Sonia R. Grover

25.1 Introduction

Although some children may present after the neonatal period, most babies are noted to have a DSD at birth when the genitalia are sufficiently ambiguous that immediate sex assignment by the midwife is difficult. This distressing situation needs a multidisciplinary team to manage the various psychological, psychosocial, hormonal and surgical issues (Houk et al. 2006).

Our hospital has been a tertiary centre specialising in DSD management for many years, and we continue to offer surgical intervention to most patients with DSD. Reasons in favour of early surgery include the maternal oestrogenic effect on the genitalia, reduced risk of urinary tract infections and satisfactory long-term results, which are described in this chapter (Lean et al. 2005; Warne et al. 2005; Crawford et al. 2009). It is our opinion that early surgery has psychological benefits for the child, as it allows them to grow up with more normally appearing genitalia, which reduces psychosocial and psychological stigma associated with DSD and also minimises parental anxiety. Another recently appreciated issue is that early surgery has a significant psychological benefit as the child is unable to form long-term memories of the abnormality or treatment thereof and hence has no long-term traumatic hospital experiences in their memory bank (Jones et al. 2009).

Currently, there remains a significant controversy surrounding early intervention in DSD, and for this reason most infants in Australia and New Zealand whose families want surgery in infancy, are managed in our centre. We offer early surgical intervention as part of a multidisciplinary management strategy with an holistic treatment plan. Although early surgery remains controversial, this chapter describes our short-term, medium-term and long-term outcomes, which we propose justify continuation of our current practice.

25.2 Short-Term Results

In the first study reported in this chapter, we describe the results of early intervention in our patients who were aged 5–10 years at the time of assessment (Crawford et al. 2009). The records of children born between 1997 and 2003 (aged 5–10 years at the time of study) were reviewed. The diagnosis, date of birth and dates of surgical intervention were recorded. The institutional ethics committee gave permission for us to collect extra information from these families when they came for their regular review. After informed consent, the children were examined and the genitalia scored on a modified scale initially used by Creighton et al. (2001), and they also completed the PedsQL

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paediatric quality-of-life inventory (4.0) (Varni et al. 2001, 2002, 2003). In addition, parents also completed the parent-report version of the quality-of-life inventory, as well as the gender identity questionnaire for children (GIQC) (Johnson et al. 2004).

The physical examination included evaluation of gross anatomical and cosmetic factors using the following criteria: symmetry of the genitalia, clitoral size and position, number of perineal openings and size of the labia majora and minora. Males were evaluated for stretched penile length, testicular volume, symmetry of the genitalia, presence of chordee, position of the urethral meatus, scrotal position and degree of fusion and location of the testes within the scrotum. An overall cosmetic score for the genitalia was given for both males and females from good, to satisfactory or poor. 'Good' was determined as the genitalia appeared normal with no abnormal features. 'Satisfactory' was described as up to two minor abnormalities, but unlikely to be judged as abnormal by a non-medically trained person. 'Poor' was defined as the genitalia appeared abnormal, with three or more abnormal features.

The PedsQL Generic Score Scales (4.0), for both child and parent questionnaires, have been validated and contain 23 items divided into physical (8 items) and psychological (15 items) domains. Each question addresses whether or not an item has been a problem in the last month on a score from nought (never a problem) to four (always a problem). The items are then scored in reverse and transformed into a scale of 100 so that higher scores indicate better quality of life.

The gender identity questionnaire (GIQC) is a validated parent-report questionnaire designed to screen for a gender identity disorder in paediatric populations (Johnson et al. 2004). The questionnaire contains 16 items addressing a range of sexual behaviours, and each one of these is scored on a 5-point scale: higher scores indicate a same-gender behaviour, and lower scores indicate cross-gender behaviour.

Fifty-four children were identified from the medical records to be eligible for participation in the study. Ten patients were lost to follow-up, and three patients refused to participate. Sixteen girls had congenital adrenal hyperplasia, two had ovo-testicular DSD and one had XX virilisation. The diagnoses in the boys included five with 45,X/46,XY partial gonadal dysgenesis, three PAIS, three with ovo-testicular DSD and six with XY undervirilisation. There were five others with vanishing testis syndrome, Klinefelter syndrome, 5α-reductase-2 deficiency, 17β-HSD deficiency and placental insufficiency. The mean age at first surgical intervention was 13.2 months, and the mean age at follow-up was 7.5 ± 2.1 years.

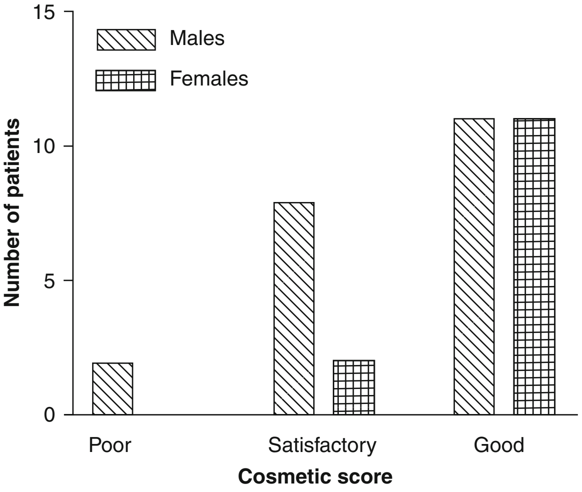

Fig. 25.1 Cosmetic results of early surgery by gender in 5–10 year olds (Reproduced with permission from Crawford et al. 2009)

Anatomical evaluation was undertaken on 13 of the 19 females, with 11 receiving a good cosmetic score and two receiving a satisfactory score. Twenty-one boys were examined, with 11 scored as good, 8 satisfactory and 2 poor (Fig. 25.1). The most commonly found abnormal feature in the boys was short stretched penile length. In many cases stretched penile length was deficient, with only 10 out of 21 boys having penile length within two standard deviations of the normal. Quality-of-life questionnaires showed that both children and parents rated their physical quality of life as being close to reported values for healthy children, with the only exception being the boys who rated their physical quality of life as lower (Crawford et al. 2009). For psychosocial quality of life, both children and their parents rated this lower than for healthy children, with boys scoring 67 and girls 76 (compared with normal values of 70 and 79, respectively) (Fig. 25.2a, b).

The mean scores for the gender identity questionnaire differed between females and males. The mean score for girls was 3.56, compared with 3.95 for boys. One male and three females (with CAH) had a score of three or less, which is in the range where there may be a risk of a gender identity disorder later in life (Fig. 25.3).

These short-term results show that early genital surgery produced satisfactory cosmetic results for

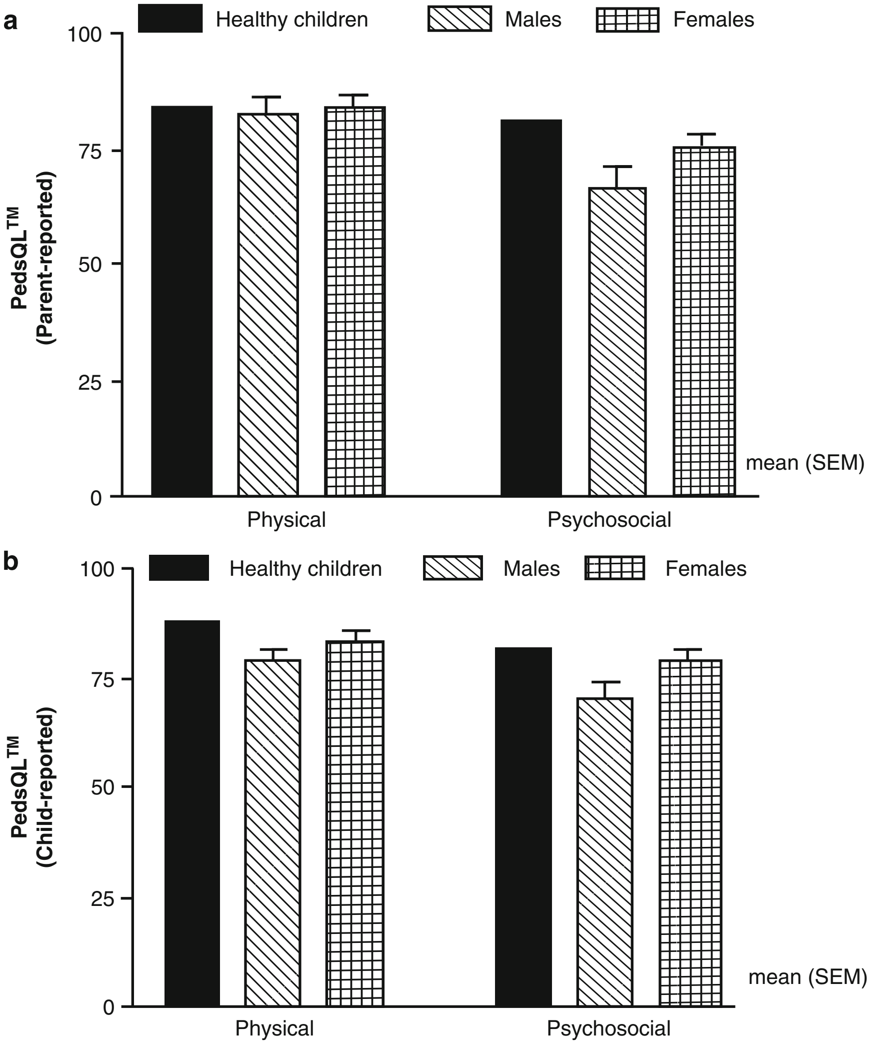

Fig. 25.2 (**a**) Parent-reported PedsQL™ scores: healthy children (Varni et al. 2003) (*solid black bar*), male DSD group (*striped bar*) and female DSD group (*cross-hatched bar*). (**b**) Child-reported PedsQL™ scores: healthy children (Varni et al. 2003) (*solid black bar*), male DSD group (*striped bar*) and female DSD group (*cross-hatched bar*) (Reproduced with permission from Crawford et al. 2009)

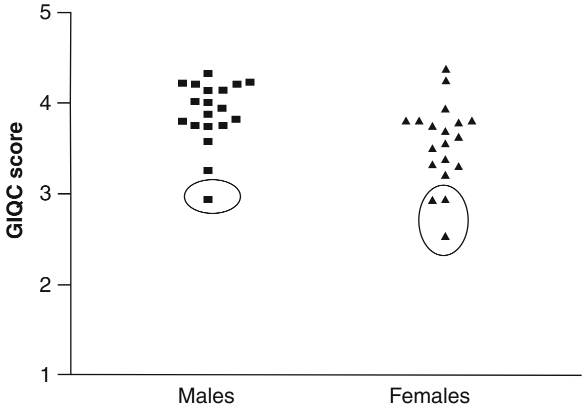

Fig. 25.3 Gender Identity Questionnaire for Children (*GIQC*) by gender. Data points within circles represent those children at risk of gender dysphoria or gender identity disorder. The three females with low scores had CAH, while the boy had PAIS

100% of females and 90% of males. More importantly, when surgery is part of an holistic management plan, an early intervention strategy appears to result in minimal impairment of quality of life or risk of gender dysphoria. The finding that the majority of our younger patients had acceptable cosmetic results agrees with recent reports in the literature. Roll et al. (2006) found that 13 out of 19 patients had excellent results and 6 out of 19 had good cosmetic results on a 4-point scale.

The physical quality of life of these children, reported both by themselves and by their parents, was in the same range as that reported by normal children (5–7 years of age) except for males who had a lower physical quality of life. On the psychosocial scale, girls and their parents reported quality of life to be only slightly lower than that reported by normal children, while both boys and their parents had significantly lower psychosocial quality of life, which is probably related to the poorer cosmetic results related to the micropenis in the boys.

The gender questionnaire showed that these children had more cross-gender behaviour traits than normal children, but the majority were not at serious risk of gender dysphoria. This is consistent with other studies of gender behaviour in boys with PAIS (Jurgensen et al. 2007) and in girls with CAH (Berenbaum and Bailey 2003). This behaviour is thought to be due to prenatal hormone exposure, which is well described in girls with CAH, although after puberty they did not experience higher levels of gender dysphoria (Zucker et al. 1996).

Although some patients were lost to follow-up, the records showed that these underwent fewer operations and were slightly older than those that were reviewed, suggesting that non-participants may actually have experienced better outcomes than those seen in the clinic. Many of these patients lost to follow-up were from interstate or overseas.

This review of short-term results supports continuation of early surgical intervention in DSD. When part of an holistic management plan, surgery produces good cosmetic outcomes and minimal impairment of quality of life.

25.3 Medium-Term Results

We have recently undertaken a medium term follow-up of our patients with DSD to examine the anatomical and cosmetic outcomes following early surgery with feminising genitoplasty (Lean et al. 2005). Patients were identified through the medical records who had undergone feminising genitoplasty between 1970 and 1991, so that the age at review was 13–33 years. All girls and young women were reviewed in the paediatric and adolescent gynaecology clinic for follow-up. As part of their routine outpatient review, examination was undertaken with informed consent. The patient held a hand mirror to enable herself to view the perineum while examination was being performed. A standard genital examination and assessment was carried out as modified from Creighton et al. (2001). This included scores for symmetry and overall genital proportions, clitoral position and size, appearance of vaginal introitus and labial appearance and proportions (from normal to full fusion). The quality of genital skin and the distribution of pubic hair was also assessed. Overall, cosmetic outcomes were assigned into categories of "good" (normal genital appearance unlikely to be judged abnormal by non-medical persons), "satisfactory" (two or less minor anomalies unlikely to be judged abnormal by a non-medical person) or "poor" outcome (genitalia abnormal, three or more abnormal features). Patients were divided into four groups depending on whether or not further treatment was required: no further treatment, dilatation, minor surgery or major surgery.

Table 25.1 Diagnoses and surgical procedures

Diagnosis	Number of patients	Surgery	Number of patients
CAH	15 (45)^	Clitoral reduction	23
MGD 45,X/46, XY	7 (17)	Clitoral recession	2
PAIS	5 (15)	Clitoral excision	3*
Ovotesticular DSD	0 (1)	Labial reconstruction	27
17β-HSD deficiency	3 (3)	V-Y vaginoplasty	29
Androgen exposure	1 (3)	Vaginal pullthrough	5
Pan hypopituitarism	1(1)		

Reproduced with permission from Lean et al. 2005

^The number in brackets is the total number of eligible patients

*Two clitoral excisions were done elsewhere; 1 was done at RCH in 1970s

Eighty-two patients were identified from the medical records, and 21 of these had moved interstate or overseas and were lost to follow-up. A representative sample of 32 out of the remaining 61 patients were examined in the gynaecology clinic. Of those patients who were not examined, they had a similar range of diagnoses as those that were seen and their surgical management was identical to those that were seen in the clinic.

The diagnoses of all patients and the 32 who were seen in the gynaecology clinic are listed in Table 25.1. Fifteen of these had CAH while the remaining 17 had a range of other conditions. The mean age at examination was 18.4 years (range 12–32 years), with no significant difference between those patients with adrenal hyperplasia and other diagnoses.

Ten of the 32 patients had their first operation done elsewhere before being referred to the Royal Children's Hospital in Melbourne. The types of procedure are listed in Table 25.1. Half of the patients had a planned single-stage genital reconstruction and 5 of these 16 needed vaginal dilatation in adolescence, and one patient needed

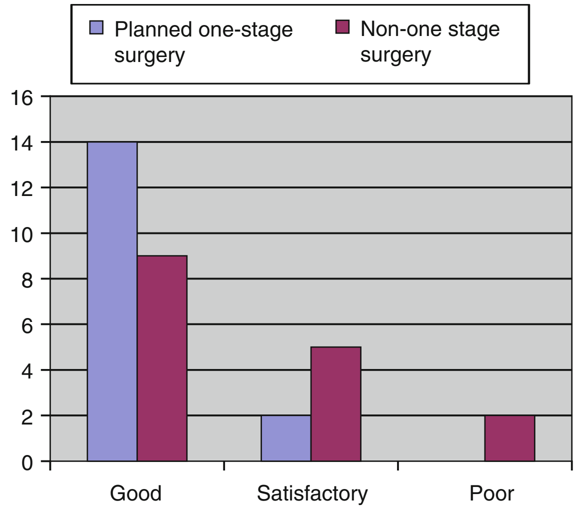

Fig. 25.4 Cosmetic outcomes in females of planned 1-stage reconstruction (*pale bar*) vs multiple stages (*dark bar*) (Reproduced with permission from Lean et al. 2005)

a repeat flap vaginoplasty at 9 years of age. One other adolescent girl had a further reduction of the bulk of the corpus spongiosum and corpora cavernosa and a vaginoplasty. Of the 16 having a planned single-stage procedure, 14 achieved a good cosmetic outcome. In 17 patients where more than one genital operation had been done, 10 (59%) had a good cosmetic outcome, and 5 (29%) had satisfactory outcomes. Only 2 patients (12%) had poor cosmetic outcomes (Fig. 25.4).

Half the patients had had surgery before 2 years of age, and 12 of these had a good outcome, which was the same as those having surgery after 2 years of age.

Twenty-nine out of 32 patients had undergone clitoral reduction and vaginoplasty, and 27 had also had surgery to the labia. The majority of patients whose surgery was done by one of the dedicated surgeons in our team appeared to have a normal clitoris on examination. By contrast, those who had undergone reduction of the clitoris elsewhere by non-specialised surgeons showed the poorer outcomes, with the clitoris being either too small, too big or absent (Fig. 25.5).

Overall cosmetic outcome for the genitalia was graded as good in 23 out of 32 patients and was satisfactory in 7 with only 2 patients (6%) having an overall poor cosmetic appearance. Of the 22 patients who had been operated on at the Children's Hospital entirely, 19 had a good outcome and 3 had a satisfactory outcome. When overall and cosmetic outcomes were analysed on the basis of location of the initial surgery, it was found that those patients who had had their initial surgery at the Royal Children's Hospital had much better outcomes (18/22 compared with those who had had their initial surgery elsewhere 3/10) Table 25.2.

Table 25.2 Anatomic outcomes of feminising genital surgery

	Normal	Abnormal
Clitoris	24	8 (1 large, 3 small, 4 absent)
Clitoral position	30	2
Vaginal introitus	20	12 (small)
Introital position	30	2
Labia majora	26	6 (1 small, 5 poor/scrotal)
Labia minora	15	17 (4 small, 2 poor, 11 absent)

This audit of medium to long-term surgical results shows that planned one-stage surgery done in an institution with a dedicated team gave a better outcome than multistage surgery, which appeared to be associated with increased scarring and fibrosis.

These results support concentration of patients to a referral centre so that surgeons can maintain expertise, as when this is done the results in this study and in others are good (Vidal et al. 2010). Sotiropoulos et al. (1976) reviewed 32 females between 5 and 22 years of age and reported good functional and cosmetic results following clitoral recession or resection. In their cohort, many girls who had vaginoplasty done before puberty required surgical revision in adolescence. Alizai et al. (1999) has also reported the need for repeat vaginoplasty in adolescence, with poor results correlating with surgeons' lack of expertise and experience. This correlation of surgical skill with outcome is consistent with our own results, where the poorest results were observed in surgery done by nonspecialised surgeons. The different outcomes for vaginoplasty may relate to the different techniques used over the 10–30 years. Other authors also reported satisfactory outcomes with single-stage infantile repair, but have not provided a standardised assessment method (Azziz et al. 1986; Gonzalez and Fernandes 1990).

The results reported from centres in United Kingdom, particularly those by Creighton et al., are in marked contrast to those reported here (Creighton et al. 2001). Using similarly objective measures to those used in this study, they found that 41% of patients had poor cosmetic outcomes and 98% required further treatment for cosmetic reasons. Moreover, of those women who had planned single-stage surgery in infancy or childhood, 89% required further major surgery. This is in stark contrast to our own studies where very few required

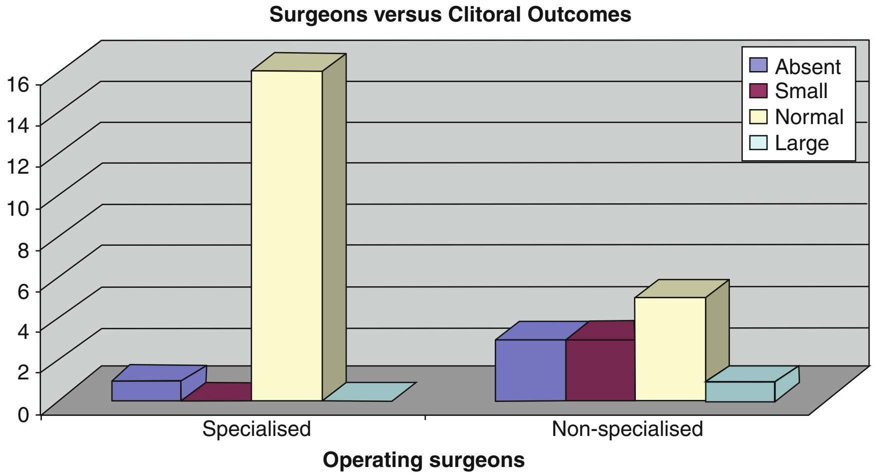

Fig. 25.5 Anatomic outcomes for clitoris vs experience of surgeon (*dark grey bar*, *absent; black bar*, small; *white bar*, normal; *light grey bar*, large) (Reproduced with permission from Lean et al. 2005)

further major surgery; in fact, only 2/32 patients required further major surgery, 3 patients required minor vaginal surgery and 13 required dilatation. The reason for these very different results is probably related to the fact that the management of these patients in the Royal Children's Hospital has been centralised into a team of experts for many years, while the patients reported by Creighton et al. (2001) had been referred from various centres in the United Kingdom, and were presumably biased to include those with poorer outcomes. Another difference between this review and the Creighton study is that our own patients were mostly examined in outpatients with the patient involved in the examination with a mirror, while in the series of patients described by Creighton et al., many of these had examination under anaesthesia. We found that examination under anaesthesia was infrequently required, and that examination in the clinic allowed the young woman to maintain some sense of self-control and autonomy.

Although our sample size was relatively small, and only half of those patients who were eligible were actually examined, the population seen was deemed to be representative of the total population of patients. One of the arguments in favour of early surgery is avoidance of long-term memory of the surgical procedure. This has not been studied often in patients having feminising genitoplasty but has been reviewed in our own clinic in patients raised as boys having hypospadias repair (Jones et al. 2009). When boys had surgery at an early age which was completed prior to primary school, they demonstrated no serious psychological disturbance and no memory of the intervention at 13–15 years of age (Jones et al. 2009).

These results show that operations in early infancy done in a referral centre can produce satisfactory anatomical and cosmetic outcomes with a very low incidence of the need for major secondary surgery in adolescence. Although some adolescent girls needed dilatation of the vagina, this was done at the time that they were able to co-operate in the management and it was perceived by them to be far superior to the need for further surgery. Single-stage surgery, if done by surgeons in an expert referral centre, can have a positive impact on anatomical and cosmetic outcome, obviating the need for major surgery in adolescence.

25.4 Psychosocial and Psychosexual Outcomes in Young Adults

We have had an integrated team involved in the management of patients with DSD and we were pioneers in promoting full disclosure of the diagnosis to parents from 1984. Since 1992, the multidisciplinary team has met regularly to discuss and share experience about patients and their problems. This enabled us to develop an holistic, patient-centred model of care which has permitted us to provide parent support and encourage development of professional parent discussion groups and counselling groups, as well as the production of educational material. Since 1996, we have aimed for full disclosure to patients as well as parents.

Although we felt we were doing well with their long-term management of psychological and psychosexual problems, outcomes in our young adult patients were unknown. We therefore decided to review our patients from 18 to 32 years of age to try and assess whether they were doing well enough on psychosocial and psychosexual issues (Warne et al. 2005).

Table 25.3 Diagnoses and identified gender of patients seen in long-term follow-up study

	Males	Females	Total
Mixed gonadal dysgenesis 45,X/46,XY (MGD)	1	1	2
Pure gonadal dysgenesis (PGD)		3	3
Congenital adrenal hyperplasia (CAH)	1	14	16
Complete androgen insensitivity syndrome (CAIS)		3	3
Partial androgen insensitivity syndrome (PAIS)	2	2	4
Vaginal agenesis		5	5
Severe hypospadias	11		11
17-β hydroxysteroid dehydrogenase (17β-HSD) deficiency		1	2
5-α reductase-2 deficiency	1		1
Post danazole therapy in utero		1	1
Cloacal anomaly		1	1
Bifid urethra and ectopic urethra	1		1
Total	17	31	50

Notes: (i) One person with CAH was assigned female and did not report identifying as male or female, and one person with 17β-HSD deficiency was assigned female now wishes to be identified as male, female, transgender and intersex. The two people (CAH & PAIS) who were assigned female and who now identify as male were included in the male column. (ii) The phenotypic similarities of women with vaginal agenesis and CAIS result in similar long-term issues, thus the sample included participants with these diagnoses

The populations of this study included patients between 18 and 32 who had been treated at the Royal Children's Hospital for a DSD. The sample, not surprisingly, comprised a range of conditions, the most common of which was CAH. We also included those boys with very severe peno-scrotal hypospadias and children with AIS, gonadal dysgenesis, as well as those girls with vaginal agenesis and other patients with rare conditions (Table 25.3). One hundred and forty-eight patients were identified on a search of the medical records, although 11 of these patients had died. From our initial list, we found that one patient had a congenital anomaly too minor to consider as part of the series and five patients had hypospadias that was not considered serious enough to be included in the DSD group. Thirty-one patients were lost to follow-up, three were excluded because they resided in remote locations and two were excluded because of intellectual disability. Of the 95 patients still potentially eligible to review, 27 declined to participate and 68 were sent to study materials and 50 of these returned completed questionnaires (Table 25.4) This gave us an overall participation rate of 53%.

To provide an adequate group of clinical control patients, we chose young people with Hirschsprung disease, which is a congenital anomaly affecting the bowel which typically requires surgery in infancy, as well as ongoing regular treatment and follow-up visits to the hospital. We found 51 patients with Hirschsprung disease in the database and of those 27 completed a questionnaire, giving a participation rate of 53%. We also had a second control group of patients with insulin-dependent diabetes mellitus (IDDM). IDDM is a chronic illness usually diagnosed in childhood or adolescence, which requires regular visits to the endocrinologist for treatment and ongoing medical advice. There were 59 patients invited to participate, and 19 completed the questionnaires, with a participation rate of 32% (Table 25.5).

After approval by the human ethics committee, all potential participants were sent an invitation letter and consent form from the relevant medical specialist involved in their care. This was followed up by a telephone call to address any unresolved issues, and then consenting participants were sent a questionnaire booklet, which was described as a quality-of-life and well-being survey, investigating the long-term outcomes of people who had been treated for conditions caused by variations in sexual development before birth. The patients with DSD were told that their responses would help provide an understanding of how medical management has affected different areas of their life. The Hirschsprung disease and IDDM groups were informed that their responses could provide a useful comparison. Completion of the questionnaires was estimated to take 1–2 h.

For statistical analysis, composite scale scores were extrapolated if the person had responded to at least the majority of items. In those instances of missing data, an average score was computed from the items that were completed. Each variable was analysed in a separate analysis-of-variance for ordinal outcome variables, and

Table 25.4 Study measures

Construct	Measure	Scales	Scoring	Reliability
General Health	Rand-36 Health Status Inventory (RAND-36 HSI)	3 composite scales, labelled Physical Health, Mental Health and Global Health	Standardized scale T scores are calculated using item response theory and age-based normative weighting (mean = 50, SD = 10)	Cronbach's alpha coefficient estimates ranged from 0.73 to 0.95
Interpersonal Problems	Inventory of Interpersonal Problems (IIP-32)	Eight subscales + a total score	Scores converted to standardized T scores (mean = 50, SD = 10)	Scale reliability coefficients ranged from 0.63 to 0.85.
Personality	Eysenck Personality Questionnaire Revised (EPQR)	Three scales labelled Psychoticism, Neuroticism and Extraversion	Responses on a dichotomous scale (yes/no). Items are summed to compute scale scores	Scale reliability coefficients ranged from 0.61 to 0.88.
Self-Esteem	Coopersmith Self-Esteem Inventory (SEI)	Total score	Items endorsed on a dichotomous scale ("like me" or "unlike me") generating a total score	The reliability coefficient was 0.86
Anxiety	State-Trait Anxiety Inventory, Form Y (STAI)	Measures State anxiety – a level of emotional intensity at a given moment in time + trait anxiety – a stable personality characteristic of anxiety-proneness	40 items are rated from 1 to 4, and summed to compute both a state and trait score, each having a range from 20 to 80	Reliability coefficients for the two scales were 0.93 and 0.94
Trauma Symptoms	Impact of Event Scale – Revised (IES-R)	22-item questionnaire rates stressful events The three subscales closely follow the DSM-IV criteria for PTSD, measuring avoidance, intrusion (re-experiencing) and hyperarousal, together with a total score.	Level of distress for each event is rated on a 5-point scale from 0 (not at all) to 4 (extremely). Subscale scores were computed by calculating the average score. A total scale score was computed by summing the three subscale scores	Reliability coefficients ranged from 0.84 to 0.94
Depression	Beck Depression Inventory, Short Form (BDI)	Total score	The 13 items are scored on a 4-point scale and summed to compute a total score	The reliability coefficient for the scale was 0.89
Gender Identity	Personal Attributes Questionnaire (PAQ)	The questionnaire comprises a masculinity (or instrumental) scale, a femininity (or expressive) scale, and a third masculinity-femininity scale, consisting of items considered to be socially desirable for one sex, but not the other	Each item was scored from 0 to 4, and summed to compute scale scores. The feminine items on the masculinity-femininity scale are recorded so that high scores indicate masculinity	Reliability coefficients for the scales ranged from 0.57 to 0.72
	The Bem Sex Role Inventory – Short Form (BSRI)	The inventory measures gender identity on the Masculinity-Femininity dimensional scale	Respondents rate 30 traits on a scale from 1 (never or almost never true) to 7 (always or almost always true). A difference score is then calculated, with T scores of 50 indicating a balance of masculinity and femininity	The reliability coefficient for the scale was 0.86

Body Image	Body Parts Satisfaction Scale (BPSS)	A total score is used for the 24 body parts items. A separate single item measures “Overall body appearance”	The items are rated on a 6-point scale from 1 (extremely satisfied) to 6 (extremely dissatisfied), and are reverse-scored	The reliability coefficient for the scale was 0.91
Sexual Awareness	The Sexual Awareness Questionnaire (SAQ)	The questionnaire comprises four scales, labelled Sexual Consciousness, Sexual Monitoring, Sexual Assertiveness, and Sex-Appeal Consciousness	The 36-items are rated on a 5-point scale from 0 (not at all characteristic of me) to 4 (very characteristic of me), and mean scale scores were calculated	Reliability coefficients for the scales ranged from 0.77 to 0.89
Sexual Functioning and Satisfaction	Individual items were borrowed and modified from various other inventories	Individual items measured sexual orientation, and degree of arousal, desire and pain during sexual activity	The items are reported individually, and most were rated on a 5-point Likert scale	N/A

Table 25.5 Demographic characteristics of DSD patients and controls

			Control		
		DSD	HPD	IDDM	HPD + IDDM
		N = 50	*N* = 27	*N* = 19	*N* = 46
Age	M (SD)	25.1 (4.3)	25.3 (3.8)	26.4 (3.9)	25.7 (3.8)
Gender ("that you identify with")					
Male	N (%)	17 (35.4)	18 (66.7)*	11 (57.9)	29 (63.0)**
Female		31 (64.6)	9 (33.3)	8 (42.1)	17 (37.0)
Education					
Secondary School (year 12 or earlier)		21 (42.0)	11 (40.7)	6 (31.6)	17 (37.0)
Post-school qualification – university or TAFE		29 (58.0)	16 (59.3)	13 (68.4)	29 (63.0)
Marital status					
Married/defacto		12 (24.5)	9 (33.3)	5 (26.3)	14 (30.4)
Single/other		37 (75.5)	18 (66.7)	14 (73.7)	32 (69.6)
One or more children					
Yes		7 (14.6)	5 (18.5)	4 (21.1)	9 (19.6)
No		41 (85.4)	22 (81.5)	15 (78.9)	37 (80.4)
Socio-occupational status					
White-collar		26 (70.3)	16 (64.0)	14 (87.5)	30 (73.2)
Blue-collar		11 (29.7)	9 (36.0)	2 (12.5)	11 (26.8)

Note: The DSD group is treated as the base category for comparison with the control groups
HPD Hirschsprung disease, *IDDM* insulin-dependent diabetes mellitus
$*p < 0.05$; $**p < 0.01$

Table 25.6 General health and psychosocial functioning

			Control						Total
	DSD		HPD		IDDM		HPD + IDDM		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*N*
RAND-36 HSI: Physical health composite	46.5	(10.7)	48.8	(12.1)	46.1	(12.9)	47.7	(12.4)	94
RAND-36 HSI: Mental health composite	47.9	(11.7)	48.6	(12.9)	47.8	(12.8)	48.3	(12.7)	93
RAND-36 HSI: Global health composite	47.2	(10.9)	48.1	(13.1)	46.4	(13.5)	47.4	(13.1)	91
Beck Depression Inventory	4.5	(5.1)	3.7	(4.6)	5.6	(6.0)	4.5	(5.2)	95
Coopersmith Self-Esteem Inventory	62.8	(19.6)	77.0**	(20.5)	62.7	(23.9)	71.1	(22.8)	96
STAI: State anxiety	38.4	(11.6)	34.0	(12.7)	40.0	(14.9)	36.5	(13.8)	96
STAI: Trait anxiety	41.3	(11.1)	35.5*	(12.5)	41.6	(14.2)	38.0	(13.4)	96
EPQ-R short version: Psychoticism	3.2	(2.1)	3.2	(2.4)	2.5	(2.0)	2.9	(2.3)	95
EPQ-R short version: Extraversion	8.2	(3.4)	9.5	(2.6)	5.3**	(3.8)	7.8	(3.7)	95
EPQ-R short version: Neuroticism	6.4	(3.4)	5.3	(3.5)	6.1	(3.1)	5.6	(3.3)	95
Inventory of Interpersonal Problems: Total score	55.4	(10.3)	49.3*	(8.0)	55.9	(10.2)	52.1	(9.5)	95
Impact of Event Scale Revised: Total score	4.6	(2.7)	3.6	(2.1)	3.7	(2.8)	3.6	(2.4)	94

Note: The DSD group is treated as the base category for comparison with the control groups
$*p < 0.05$; $**p < 0.01$

logistic regression for dichotomous outcome variables; 95% confidence intervals were presented around the mean difference and an odds ratio was calculated.

At the time of data collection, the mean age of participants was 25 years of age (range 18–32 years). Although there were more females in the DSD group than in the control groups, there were no significant group differences in age, education or socio-demographic variables (Table 25.5).

There were no major differences in physical or mental health, depression, current anxiety, neuroticism, psychiatric or stressful life events (Table 25.6). The DSD participants were satisfied with their overall body appearance, although males with DSD were less satisfied than controls with the size and appearance of their external genitalia. The DSD patients were less likely to experience orgasm, and tended to experience more pain during intercourse,

Table 25.7 Psychosexual measures

		DSD		Control						Total
				HPD		IDDM		HPD + IDDM		*N*
BPSS: Satisfaction with size of sex organs	M(SD)	3.8	(1.6)	4.6*	(0.9)	4.3	(1.4)	4.5*	(1.1)	90
BPSS: Satisfaction with appearance of sex organs	M(SD)	3.8	(1.6)	4.7*	(0.8)	4.2	(1.5)	4.5*	(1.1)	90
BPSS: Satisfaction with overall body appearance	M(SD)	4.0	(1.3)	4.6*	(0.8)	3.9	(1.3)	4.3	(1.1)	92
BPSS: Total score (for all 24 body part items)	M(SD)	105.9	(16.4)	110.0	(12.3)	104.4	(17.2)	107.7	(14.6)	93
SAQ: sexual-consciousness subscale	M(SD)	2.6	(0.9)	3.1*	(0.7)	2.5	(0.7)	2.9	(0.7)	92
SAQ: sexual-monitoring subscale	M(SD)	2.1	(0.8)	2.1	(0.7)	2.1	(0.9)	2.1	(0.8)	92
SAQ: sexual-assertiveness subscale	M(SD)	1.7	(0.8)	2.0	(1.0)	1.4	(0.9)	1.7	(1.0)	92
SAQ: sex-appeal-consciousness subscale	M(SD)	1.4	(1.2)	1.7	(1.0)	0.9	(1.2)	1.4	(1.1)	93
Males: PAQ Masculinity (or instrumental) scale	M(SD)	21.3	(5.3)	21.7	(5.3)	18.1	(4.9)	20.3	(5.4)	45
Females: PAQ Masculinity (or instrumental) scale	M(SD)	21.1	(4.1)	22.6	(3.8)	19.6	(4.2)	21.2	(4.2)	48
Males: PAQ Femininity (or expressive) scale	M(SD)	21.8	(4.1)	22.9	(4.5)	21.7	(3.4)	22.4	(4.1)	45
Females: PAQ Femininity (or expressive) scale	M(SD)	22.3	(4.4)	25.0	(2.6)	25.0	(3.7)	25.0*	(3.1)	48
Males: PAQ Masculinity-Femininity scale	M(SD)	14.7	(3.6)	15.8	(5.3)	13.9	(4.5)	15.1	(5.0)	45
Females: PAQ Masculinity-Femininity scale	M(SD)	14.8	(3.7)	15.7	(4.2)	13.0	(5.8)	14.4	(5.1)	48
Males: BSRI Difference score (femininity – masculinity)	M(SD)	49.7	(10.5)	49.7	(12.2)	54.1	(11.8)	51.4	(12.1)	45
Females: BSRI Difference score (femininity – masculinity)	M(SD)	49.8	(9.8)	55.9	(6.3)	53.4	(12.4)	54.7	(9.4)	49
Males: Difficulties achieving erection										45
More than half the time	%	6.3		5.6				3.4		
Sometimes (about half the time)	%	6.3		11.1				6.9		
Less than half the time	%	87.5		83.3		100.0		89.7		
Females: Become lubricated ("wet") during sexual activity										46
More than half the time	%	77.4		85.7		87.5		86.7		
Sometimes (about half the time)	%	9.7				12.5		6.7		
Less than half the time	%	12.9		14.3				6.7		
Experience orgasm (climax) during sexual activity	M(SD)	3.9	(1.1)	4.3	(1.0)	4.4	(0.9)	4.3*	(0.9)	87
Experience any pain during intercourse	M(SD)	1.9	(1.1)	1.6	(0.9)	1.4	(0.6)	1.5	(0.8)	85
Experience any difficulty with penetration	M(SD)	2.2	(1.5)	1.6	(0.9)	1.4*	(0.6)	1.5**	(0.8)	86
How many times during the last month you have had sexual activity										93
Less than several times a week	%	50.0		23.1*		26.3		24.4*		
Several times a week or more	%	50.0		76.9		73.7		75.6		
Sexual preference										91
Heterosexual	%	84.8		92.3		94.7		93.3		
Bisexual	%	8.7		3.8				2.2		
Lesbian/gay	%	6.5		3.8		5.3		4.4		
How enjoyable are sexual activities for you?	M(SD)	3.9	(1.0)	4.3	(0.9)	4.0	(0.7)	4.2	(0.9)	89
Level of sexual desire										92
High or very high	%	62.5		68.0		68.4		68.2		
Moderate	%	29.2		32.0		15.8		25.0		
Low, very low or none at all	%	8.3				15.8		6.8		

Note: The DSD group is treated as the base category for comparison with the control groups
*$p<0.05$; **$p<0.01$

and also had more difficulties with penetration than the combined control groups. In addition, they were also more likely to have less frequent sexual activity than the control groups. However, DSD patients did not differ from the control groups in the level of sexual desire or enjoyment of sexual activities (Table 25.7). These results show that patients with DSD have positive psychosocial and psychosexual outcomes, even when treatment was begun more than 30 years ago, although some problems persist with sexual activity.

This detailed review of long-term psychosocial and psychosexual outcomes shows that young adults with DSD who were treated at the Royal Children's Hospital had relatively good outcomes. They did not differ from young adults with Hirschsprung disease or diabetes on such measures as general physical and mental health or post-traumatic stress disorder symptoms. More importantly, the DSD patients showed mean scores on most of these measures that were not indicative of any clinically significant problem likely to impede general life functioning. The DSD patients reported lower self-esteem and higher anxiety traits than the Hirschsprung patients, indicating that they tended to be more self disapproving and perceived stressful situations as more threatening. However, they scored no more severely than those with other chronic illnesses such as diabetes. Overall, these findings are consistent with earlier reports of positive psychosexual and general health outcomes in women with CAH and other forms of DSD.

The males tended to report lower levels of satisfaction with their genitalia than control groups, which is probably related to genital size similar to that reported by Gupta et al. (2010). In addition, compared to other groups, the DSD patients reported more problems during sexual intercourse. Despite this, DSD patients did not differ from the control groups on self-reported enjoyment of sexual activity or level of sexual desire.

One of the weaknesses of a longitudinal study such as this is the concern that non-participants may have had a poorer outcome. However, in this study, a participation over 53% is comparable with many other studies in the literature. Also, the similar or lower rates of participation in the two control groups suggests that participation was a function of the method of contact rather than the underlying disorder.

Despite some of these limitations, this long-term review indicated a generally positive psychosocial and psychosexual outcome, which is in contrast to many other studies reported in the literature (Creighton et al. 2001; Minto et al. 2003; Schober 2001; Reiner and Gearhart 2004). This supports an holistic approach by a multidisciplinary specialised team, which we feel strongly should include mental health and social work, working in close liaison with support groups. The readiness of clinicians in our group to disclose and openly discuss the diagnosis and broader issues, such as sexuality, is likely to be important in the long-term outcome. As all the participants in this follow-up study had genital reconstructive surgery in infancy or early childhood, the results did not support a change in this practice.

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Long-Term Outcome of Disorders of Sex Development (DSD): A World View

26

Garry L. Warne

26.1 Introduction

The management of disorders of sex development (DSD) has been a problem area for years, partly because clinicians have started to see that not all of their patients grow up to be happy adults content with the gender assigned to them at birth, and partly because of the vigorous activities of patient-advocacy organizations who have publicized their unhappiness and disagreement about current practices to the world at large and to politicians in particular. Results from a large number of long-term outcome studies have been published in the last decade and this chapter gives an overview of what we now know and what we still do not know about how to obtain a good outcome for our patients. Many studies have focused on a particular disorder and there have been more about congenital adrenal hyperplasia (CAH) and complete androgen insensitivity (CAIS) than any of the other conditions, even though mixed gonadal dysgenesis is probably more common than CAIS. This is because researchers have wanted to know about the effects of hormones on the brain. There have been studies from a number of different countries, and cultural differences come to the fore in disorders affecting sex and gender. Very few studies have been done in Africa or East Asia so far. Long-term outcome should be studied in every treatment centre, but there is a great need for study instruments to be developed that would be robust enough to use in a range of different cultural settings and languages. The studies show that while many patients fare well and are leading productive lives, gender dysphoria has been underestimated in the past and that gender counselling as well as sexual counselling should be part of the multi-disciplinary service available to patients with DSD. More emphasis is also needed on strategies to prevent the development of germ cell cancers. Urological problems in both males and females with DSD have been underestimated and deserve more attention.

The long-term outcome of disorders of sex development (DSD) has been the subject of intense interest for decades. A report from the Dominican Republic (Imperato-McGinley et al. 1979) revealed that XY individuals with 5α-reductase-2 deficiency were initially raised as females but underwent spontaneous transition to male gender identity during adolescence. Reports in the 1990s from Australia (Warne 1992) and the United States (Meyer-Bahlburg et al. 1996) described girls with congenital adrenal hyperplasia who had become so virilised that they could no longer accept their female gender identity. The advent of the internet in the late 1990s (Warne et al. 1998) led to the establishment of patient-advocacy organizations such as the Intersex Society of North America and the Androgen Insensitivity Support Group; some members of which became high-profile critics of prevailing western medical practices in respect of DSD which advocated feminising genitoplasty regardless of other factors, and defended keeping sensitive medical information hidden from patients and even parents. Their vigorous media campaigns were, however, based on the effect their condition was having on their lives as adults and were driven by passion. An indignant

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medical profession protested at being attacked in this way, but until that time, very few long-term outcome studies had been carried out to allow either side of the debate to speak with authority about numbers. The need for these studies became obvious. Most of the long-term outcome studies identified for this review were published after 2000.

What is the value of a well-designed long-term outcome study? It may provide evidence that an intervention was or was not beneficial for the patient. It provides a basis for prediction and is therefore useful when protocols are being revised. It yields information about the current situation of the patients and what their on-going needs are. It may reveal unforeseen events that occurred. It speaks about how a disorder continues to affect people's lives as they reach adulthood, middle age, and beyond. It might provide a reflection about the cultural context in which the study took place, in addition it measures how well a particular treatment centre is doing and may allow different centres to compare their results.

What is actually measured? The data will record selected aspects of the current situation of a cohort of patients, such as their physical health, mental health, social integration and status, sexual health, fertility, etc. They might record important events in the patient's journey and explore how the person managed threats as well as successes, devised strategies, used help that was offered, and identified things that were unhelpful or actually harmful.

What are the limitations? The report can only describe the participants in the study; non-participants keep their information to themselves and they could be different from those who participated. Studies of DSD never achieve 100% participation – patients die or are lost to follow-up, they are often unwilling to participate for various reasons, or they may be incapable of participating. The term DSD covers a wide range of conditions, many of which are rare, and conclusions from studies that attempt to consider them as one group may be different from those derived from studies of well-defined, disorder-specific groups. Long-term outcome depends on many factors that may or may not be related to the medical care that was provided, so in any particular study, the results can really only reflect a whole package: it is difficult, if not impossible, to evaluate individual components of the overall therapy. Quantitative data may not capture the true essence of the problem and the question 'Why did some do better than others?' may need to be the subject of additional, qualitative research. Finally, the study may not be 'owned' by the group being studied and it may therefore not be looking in the areas that they would want studied (health professionals may want to find justification for what they did and may downplay the intense suffering of a small minority).

DSD have recently been re-classified and the new nomenclature (Hughes 2008) will be used in this review.

26.2 46,XX DSD

26.2.1 Congenital Adrenal Hyperplasia (21-Hydroxylase Deficiency) (CAH)

The history of all women with classical CAH is of exposure to high levels of adrenal androgens in utero and of being born with ambiguous, even male genitalia, but also with ovaries and a uterus. Typically, they then had surgery during childhood to reduce the size of the clitoris and to divide the fused labia, allowing the vagina to open onto the perineum and removing any urinary obstruction that could have caused backfilling of the vagina. The hormonal management of CAH requires medications (a glucocorticoid and usually a mineralocorticoid) to be taken several times a day every day of their lives and regular attendance for medical reviews and blood tests. The parents were probably greatly distressed following the birth of their child; anxiety, guilt, embarrassment, and secrecy may have distanced them from family and friends.

Many long-term follow-up studies of women with classical CAH have focused on the effects of prenatal exposure of the brain to androgens in genetic females. Gender role behaviour is usually affected during childhood, sexual orientation is more often bisexual or homosexual than in the general population, but gender identity is rarely affected (Hurtig et al. 1983; Kuhnle et al. 1993; May et al. 1996; Kuhnle and Bullinger 1997; Berenbaum et al. 2004; Long et al. 2004; Dessens et al. 2005; Meyer-Bahlburg et al. 2006). Under certain circumstances, particularly when the diagnosis is delayed and androgens are not adequately suppressed over a long period during childhood, gender identity may gradually change from female to male (Warne 1992; Meyer-Bahlburg et al. 1996). This is a well-recognized phenomenon in developing countries where patients present late and due to both poverty, lack of education, and difficulty of access to essential medications do not achieve suppression of androgens in childhood (Armstrong et al. 2006; Gupta et al. 2006; Warne and Bhatia 2006; Al-Maghribi 2007). On the other hand, gender reassignment from male to female in genetic females born completely masculinised is generally successful, provided that the correct diagnosis is made in early childhood and androgen suppression is maintained thereafter (Woelfle et al. 2002; Lee and Witchel 2005).

Some authors have studied women with CAH to see if cognitive abilities are affected by prenatal androgen exposure, given that there were earlier reports that females with CAH had enhanced spatial orientation compared with non-exposed females. Females with CAH performed better than females without CAH and as well as males on targeting tasks but not on mental rotation tasks (Hines et al. 2003a). Cerebral lateralization, as measured by hand preference and hearing tests, appeared to show a shift towards right hemisphere dominance in adolescents with CAH (Kelso et al. 2000). Other authors, however, dispute these findings (Malouf et al. 2006) and report no consistent differences attributable to CAH.

Intense controversy has raged over the past decade about the ethics of performing genital surgery on infants unable to give consent. Critics of this practice argue that the surgery is un-necessary in an infant, given that the sole function of the clitoris is to give sexual pleasure. Because women with CAH nearly all had genital surgery as infants or young children, many studies focused on sexual function. All studies agree that women with CAH engage in sexual activity less frequently than women studied in control groups (Kuhnle et al. 1993, 1995; May et al. 1996), have greater degrees of pain and discomfort associated with penetrative intercourse (Warne et al. 2005a), are less fertile (Hagenfeldt et al. 2008), and have an increased risk of gestational diabetes (Falhammar et al. 2007). Women being treated for CAH have circulating androgens that are lower than normal and higher progesterone levels (Helleday et al. 1993); whether this could be related to alterations in libido is unknown. Reduced clitoral sensation is clearly a factor for some (Schober 2004) as is re-stenosis of the introitus (Crouch et al. 2008). The history of clitoral surgery and of the different types of operations used has been reviewed by Lean et al. (2007) and a startling recent discovery about the anatomy of the clitoris in normal women (O'Connell et al. 2005) raised questions about what the extent of the enlarged internal parts of the clitoris would be in women with CAH, and how this would affect the woman. Removing a source of lower urinary tract obstruction, which because of urine backflow into the vagina can predispose to recurrent urinary tract infection, is used as a justification for early surgery to separate fused labia. Women with CAH are at a greater risk of lower urinary tract symptoms such as stress and urge incontinence than other women (Davies et al. 2005), but whether this is a consequence of surgery or their original anatomical disturbance, which can include a high junction between vagina and urethra, is unclear. A single report (Claahsen-van der Grinten et al. 2006a) drew attention to the risk of ovarian adrenal rest tumours in CAH. Testicular adrenal rest tumours are common in men but ovarian adrenal rest tumours in women are, for some reason, rare. Large myelolipomas in the adrenal glands can occur in adults with poorly controlled CAH. They are benign but can haemorrhage.

Women with CAH, particularly those with the salt-losing form, have reduced fertility (Claahsen-van der Grinten et al. 2006b). One reason for this is polycystic ovarian disease (Hague et al. 1990). Other reasons are the reduced frequency of sexual intercourse and also suppression of gonadotrophin secretion by elevated serum progesterone levels.

Women with salt-losing CAH sometimes encounter a situation where suppression of hyperandrogenism requires a high dose of glucocorticoids, resulting in unacceptable side effects such as obesity, glucose intolerance, and hypertension. In this group, bilateral laparoscopic adrenalectomy has been advocated. Final judgment on this is reserved, but benefits in terms of enhanced fertility have been reported (Ogilvie et al. 2006). Final height in treated adults is slightly shorter than target height but within the normal range (Nguyen et al. 2006), except in women who had non-salt-losing CAH, presented very late with an advanced bone age, and went into central precocious puberty following the commencement of glucocorticoid therapy; they have a much reduced final height.

Quality of life in women with CAH is impaired by psychosexual difficulties (May et al. 1996; Zucker et al. 1996; Wisniewski et al. 2004; Nordenskjöld et al. 2008), many of which should be preventable. This is clearly an area where a multi-disciplinary team approach to the management of adolescent patients is required, as well as well-prepared transition from paediatric to adult care. Support and guidance from a sexual health counsellor (or the likes) would be of advantage. Girls with CAH are left to fumble through sexual difficulties themselves as there is no-one properly qualified in the general multi-disciplinary setting to address the real issues. For young people, this is the most important management aspect of CAH, but yet it is brushed over. Generally, healthcare professionals only consider whether the surgical outcomes are adequate for sexual intercourse. That is not entirely the problem. Minor degrees of clitoral enlargement do not require surgery and avoiding clitoral reduction wherever possible has been strongly advocated. For more detailed reviews, see Lee and Witchel (2002); Wiebke and Krone (2007), and Riepe and Sippell (2007).

26.2.2 46,XX Congenital Adrenal Hyperplasia (11β-Hydroxylase Deficiency)

This form of CAH accounts for 10% of all cases. It is associated with hyperandrogenism causing ambiguous genitalia in females, and the accumulation of mineralocorticoids which cause arterial hypertension. Long-term outcome depends on the success of the genital surgery carried out in childhood and control of blood pressure by glucocorticoid treatment (White and Speiser 1994).

26.3 46,XX Ovo-Testicular DSD

In 60–82% of cases, the karyotype in human ovo-testicular DSD is 46,XX (Wiersma 2004; Verkauskas et al. 2007). Others may be 46,XY, 46,XX/46,XY chimeras or have other karyotypes. The genital appearance ranges from normal male to normal female, but many have ambiguous genitalia. Both ovarian and testicular tissues coexist in the person, with the distribution of one vs. the other varying considerably between individuals (van Niekerk and Retief 1981). While an ovo-testis may have two distinct poles, an even distribution throughout the length of the gonad is commonly seen. A normal ovary containing fertile oocytes is possible on one side (most commonly the left) with an ovo-testis or dysplastic testis on the other, but the testicular element degenerates faster than the ovary and male fertility is rarely if ever possible.

Testosterone production, however, may be adequate. The risk of gonadal malignancy is low unless a Y chromosome is present in the gonad (Looijenga et al. 2007). Female sex of rearing, which preserves the chance of fertility, has been the preferred option in many cases, and in these, the testicular component is removed to prevent unwanted testosterone secretion and reduce the risk of malignancy (Damiani et al. 1997, 2005; Krstic et al. 2000; Verkauskas et al. 2007).

26.4 46,XX Testicular DSD

In this condition (formerly known as XX male syndrome), similarities to Klinefelter syndrome are very strong, although men with 46,XX DSD are shorter than men with Klinefelter syndrome and men in the general population (Vorona et al. 2007). The testes are dysgenetic and infertility is the rule. The SRY gene is expressed in some, but not all, affected individuals (Abusheikha et al. 2001).

26.5 46,XX Müllerian Agenesis Syndrome

While not associated with sexual ambiguity, the Mayer-Rokitansky-Küster-Hauser syndrome (Morcel et al. 2007) is in the spectrum of DSD. Typically, the uterus and vagina are absent but there is some variation in anatomy such as partial/incompleteMűllerian duct fusion and unilateral renal agenesis. The ovaries may be ectopic, sometimes even in the inguinal canal where they are mistaken for testes. Treatment of the vaginal hypoplasia does not always require surgery as the vagina is able to lengthen in response to stretching over time, as in regular and frequent sexual intercourse. While isolated cases of ovarian cancer have been reported, it is unclear if the overall risk is increased. Cancer in Müllerian duct remnants does not appear to be increased. Women with the condition have a range of emotional difficulties related to absence of a womb, and benefit from professional counselling. At our centre, patients have found a support group very helpful.

26.6 46,XY DSD

26.6.1 Complete Androgen Insensitivity Syndrome (CAIS)

The experience of women with CAIS has been documented very eloquently by an international patient-advocacy group (http://www.aissg.org/). In the past, the failure of doctors to disclose the true nature of the condition to them and their parents led to major difficulties and this has generated a great deal of anger and resentment. Partly, the non-disclosure was due to a paternalistic attitude but it was also due to the perceived difficulty of explaining XY chromosomes and testes to a girl without traumatizing her. This has now been overcome and full disclosure is now generally advocated and practised within a more holistic, multidisciplinary context with literature to support it (Warne 1989; Lee and Money 2004). Gender identity is female (Hines et al. 2003b) and both breast size and body shape are normal. Pubic and axillary hair is scanty or absent. Women with CAIS have no uterus, and this affects body image and self-esteem, especially if combined with a degree of vaginal hypoplasia sufficient to make penetrative sexual intercourse difficult or impossible (Wisniewski et al. 2000; Wisniewski and Migeon 2002; Minto et al. 2003). Surgery is not always necessary as repeated attempts at intercourse can effectively lengthen the vagina. There are, however, a number of surgical procedures that are used (Thomas and Brock 2007). The testes are usually in a superficial inguinal position and can be the size found in men, so that they are easily knocked or compressed against the body and can be very painful during sexual intercourse or sporting activities, or when wearing tight clothes. Sometimes, this is the reason for choosing to have them removed. There is an increased risk of testicular cancer (seminoma), but this risk, once considered to be about 9%, is now thought to be of the order of 3% and only occurs after puberty (Skakkebaek 1979; Handa et al. 1995; Sakai et al. 2000; Nojima et al. 2004; Hannema et al. 2006; Looijenga et al. 2007; Robboy and Jaubert 2007). Current recommendations would support leaving the testes in until after puberty has been completed and then either removing them (with oestrogen replacement) or instituting a careful monitoring process for the early detection of seminoma. Detected early, seminoma can be effectively treated and has a good prognosis. Intra-abdominal testes must be removed. However, many women with CAIS have had their testes removed when they were children as this is still common practice.

Women with CAIS have an increased risk of osteoporosis whether or not they have their testes (Soule et al. 1995; Bertelloni et al. 1998; Mizunuma et al. 1998; Sobel et al. 2006; Danilovic et al. 2007). Although adult circulating testosterone levels are high (about 50 nmol/l) if the testes have not been removed, the skeleton is unresponsive to testosterone and consequently bone mineral density is oestrogen dependent. Oestrogen levels in women with CAIS are higher than in men but lower than in women with ovaries. Therefore it is possible, though as yet unproven, that women with CAIS who have their testes would benefit from treatment with additional oestrogen to prevent osteoporosis (Warne et al. 2005b).

Women with CAIS, being XY, are candidates for red-green colour blindness, a disorder otherwise confined to males, and they are on average slightly taller than average women. Being an X-linked trait, CAIS may affect sisters, aunts, and other female relatives.

26.6.2 Partial Androgen Insensitivity Syndrome (PAIS)

PAIS is associated with great phenotypic diversity and the phenotype is poorly predicted from the genotype (Deeb et al. 2005). Within one family (the condition is inherited as an X-linked trait), it is possible for some individuals to have ambiguous genitalia and for others to have a micropenis (without hypospadias) and gynaecomastia. Thirty years ago, doctors were taught never to consider male sex of rearing in a child with ambiguous genitalia if it was due to androgen insensitivity, on the basis that the penis would not grow at adolescence and therefore life would be intolerable. This was an exaggeration of the true situation (Husmann 2004; Lee and Houk 2004). This policy led to great unhappiness for those who had feminising surgery and then developed with a male gender identity (Mazur 2005). One study has reported that nearly 25% of subjects with PAIS were dissatisfied with their adult gender identity, regardless of whether they had originally been assigned male or female (Migeon et al. 2002a). It should be noted, however, that in the majority, gender identity followed the sex of rearing. The policy about genital surgery in babies and children with PAIS remains controversial. Some patient-advocacy groups have called for the banning of early genital surgery, preferring to allow individuals to decide for themselves when they are old enough. We now advocate a male sex of rearing in cases of PAIS because it preserves choice, even though the surgery to create a penile urethra is much more technically difficult than feminising genitoplasty. High-dose testosterone therapy (Grino et al. 1989) has potential for enlarging the penis.

The risk of testicular cancer is high (55%) in intra-abdominal testes of males with PAIS (Hughes et al. 2006) and therefore excision is recommended. The risk for scrotal testes is considered to be lower, but still moderately high, so if they are retained, a clearly communicated risk management strategy is essential. This would involve 6-monthly palpation, biopsy looking for carcinoma in situ (CIS) after puberty, and either removal of the testis or irradiation if CIS was found. Retention of testes would be expected to be associated with the development of adolescent gynaecomastia which might require bilateral mastectomies.

26.6.3 5α-Reductase-2 Deficiency

As first described (Imperato-McGinley et al. 1979), 5α-reductase-2 deficiency causes a gradual gender identity change from female to male at puberty in a significant number of individuals, if the testes have been retained and not removed in early childhood (Cohen-Kettenis 2005a). This has made it difficult to define a policy suitable for all environments (Houk et al. 2005). Gynaecomastia does not develop. The adult penis is small. Dihydrotestosterone treatment has been given with encouraging results in children (Charmandari et al. 2001). The risk of testicular cancer appears to be relatively low. The pattern of inheritance is autosomal recessive.

26.6.4 17β-Hydroxysteroid Dehydrogenase (17β-HSD) Deficiency

17β-hydroxysteroid dehydrogenase deficiency, like 5α-reductase-2 deficiency, causes a transition in gender identity from female to male in some individuals (Rosler 2006), but the response to administered testosterone would be greater. The phenotype is only seen in genotypic males; affected females have no symptoms. The pattern of inheritance is autosomal recessive.

26.6.5 46,XY Lipoid Adrenal Hyperplasia and 46,XY, 17α-Hydroxylase Deficiency

These two forms of CAH are both extremely rare. Lipoid adrenal hyperplasia, caused by a deficiency of the steroid acute regulatory protein (StAR), is associated with a complete block in steroid hormone secretion by both the adrenals and the testes, so that all subjects, whether XX or XY, have a female phenotype (Miller 2007). The prognosis is good, once the diagnosis has been made and treatment started with both a glucocorticoid and a mineralocorticoid. Oestrogen replacement is needed to induce puberty and is continued life-long. The testes secrete Müllerian inhibitory substance (MIS/AMH) normally and therefore there is no uterus.

17α-hydroxylase deficiency (Kater and Biglieri 1994) also results in a female phenotype in genotypic males, and there is no uterus, but unlike lipoid adrenal hyperplasia, it is associated with glucocorticoid-suppressible hypertension due to the accumulation of mineralocorticoid precursors.

26.6.6 46,XY Complete Gonadal Dysgenesis (Swyer Syndrome)

Women with 46,XY complete gonadal dysgenesis differ from women with CAIS in that spontaneous breast development at adolescence does not occur. Serum FSH and LH levels are high, due to primary gonadal failure. Hormone replacement therapy is able to induce secondary sex characteristics including menses, because women with this condition have a uterus. It is possible for them to carry a pregnancy if an embryo is implanted into the uterus and appropriate hormonal support is administered. The streak gonads carry a high risk of cancer and should always be excised. Gender identity is female (McCarty et al. 2006).

26.6.7 46,XY Partial Gonadal Dysgenesis (GD)

The 46,XY form of partial GD is quite rare but is the subject of considerable interest to basic researchers studying genetic regulation of gonadal differentiation, who are now applying new gene discovery strategies including micro-array. Patients are highly sought-after for this reason. More commonly, partial gonadal dysgenesis is associated with a 45,X/46,XY mosaic karyotype and discussion about long-term outcome will be found later in this chapter.

26.6.8 Persistent Müllerian Duct Syndrome

There are no long-term outcome studies on this very rare condition which is due either to mutations in the gene for Müllerian inhibitory substance (MIS/AMH) or in the MIS/AMH receptor gene. The usual anatomy is that the two vasa deferentia are enclosed within the lateral walls of the uterus and the testes are found in inguinal hernias. Complete removal of the uterus is contraindicated because it destroys any chance of spontaneous fertility by damage to the vas deferentia where they are located in the lateral wall of the cervix.

26.7 46,XY Cloacal Exstrophy

Genetic males with cloacal exstrophy have normal testes but the penis is severely hypoplastic and bifid, even absent. A generation ago, they would have had their testes removed and female genitalia constructed, then raised female. The long-term outcome was disastrous; most of those treated in this way grew up with an unequivocally male gender identity (Reiner and Gearhart 2004).

26.8 Sex Chromosome DSD

26.8.1 45,X/46,XY Partial Gonadal Dysgenesis

This condition, often referred to as mixed gonadal dysgenesis, is one of the two most common causes of ambiguous genitalia and until 1990, most endocrinologists thought that it was invariably associated with ambiguous genitalia, which is far from true. Follow up of 92 patients in whom this karyotype had been detected by antenatal testing revealed that 95% had a normal male phenotype and of these, 27% had abnormal gonadal histology (Chang et al. 1990). The risk of malignancy in the group with male phenotype remains unclear; a strategy has been proposed for management, involving close monitoring and testicular biopsies after puberty has been completed (Müller et al. 1999).

Endocrinologists and surgeons are familiar with the 5% of 45,X/46,XY foetuses who are born with ambiguous genitalia and who represent just under half of all babies with ambiguous genitalia. There is considerable phenotypic variation, but the most common gonadal phenotype would be of a testis on one side and a streak gonad on the other (Telvi et al. 1999). Ovo-testicular DSD is also part of the spectrum. Streak gonads which are intra-abdominal carry a high cancer risk and should always be removed. The scrotal testis is also dysgenetic and it too has a high risk of cancer, but patients raised male want to keep the testis if possible and therefore need close monitoring by palpation, ultrasound, and biopsy carried out at appropriate times. A uterus is present in 75%, and because of this, the female sex of rearing may have been chosen to allow the possibility of having a baby through assisted reproductive technology. Turner syndromic features are found in some individuals. Others have short stature and are considered for growth hormone therapy (Richter-Unruh et al. 2004). More often than not, gender identity in adulthood conforms to the sex assigned at birth (Cohen-Kettenis 2005b; Warne et al. 2005a; Szarras-Czapnik et al. 2007) but psychological outcomes for males appear to be slightly better than for females. Males born with perineal hypospadias, however, have more long-term urological problems, which reflect the difficulty of constructing a penile urethra from tubes constructed from skin, joined end to end (Warne et al. 2005a).

26.8.2 47,XXY Klinefelter Syndrome with Genital Ambiguity

Although genital ambiguity is not usually a feature of Klinefelter syndrome, it does occur (Lee et al. 2007) and can be associated with gender dysphoria.

26.9 Discussion

In preparing this review, I asked several people who have lived with a DSD all their lives how they would define a good long-term outcome. A middle-aged woman with AIS replied: ‘Feeling at home in one’s body, at peace with oneself as a whole person, happy to have been born/created, satisfied with HRT (hormone replacement therapy) if it has been necessary, to be able to enjoy sexual relations should one desire to enter into them, positive view of medical intervention received over the years, or with the process and results of coming to terms with the trauma.' A man born with ambiguous genitalia due to a form of CAH commented: 'It has taken me years to feel comfortable with the body I have today. I don't really feel at home. I am a guest who has learned to make myself comfortable in someone else's house but I will never be the one who owns this home. It is a house but not a home.' From these statements, it appears that perceptions of self, body image, identity, sexuality, comfort with the appearance of the body, relationships with partners and with the medical profession, and a sense of being valued in their social contexts are all markers of a good long-term outcome.

The scientific studies that have been conducted have tried to measure qualities like body image, satisfaction with the body and the genitalia, sexual feelings and sexual activity, general health, mental health, and broadly, quality of life. They reveal that the quality of life for many people with DSD, while not perfect, is satisfactory or good. There has been a much greater recognition in the last 10 years that many young people with DSD grow up not feeling comfortable in their bodies; in particular, they are not sure about their gender identity. A small percentage of these are ultimately unable to accept the gender they grew up in, and they take action to change it. Counselling about gender has to become a part of the service provided to every DSD patient after puberty.

Little information is available about how to help people born with atypical genitalia to build the self-esteem needed to establish healthy intimate and sexual relationships.

A middle-aged woman with complete AIS disclosed to a group of similarly affected women that in her youth, the question that had troubled her most was 'Would there be someone out there to love me?' It is therefore not enough for long-term follow-up studies to focus on the particular, e.g., clitoral sensation, without asking questions about the existential position of the whole person. 'This can't be emphasized enough. People can have had excellent surgical outcomes and very good pathology results throughout their lives, but still have psychological difficulties. We live with the knowledge that we produce too much testosterone but do not know to what extent the testosterone has had an impact on our outward appearance and how visible this is to people around us (i.e., if we hadn't been born with CAH or other DSD what would we have looked like physically, not just considering genitalia)' (Claire Henderson, personal communication 2008).

Disorders of sex development present many challenges for people living with the conditions, their parents, and the health professionals who care for them (Slijper et al. 1998; Thyen et al. 2005). It is an advance that so many centres are reporting long-term outcome data and the fact that these reports are not only from centres able to devote a high level of human and technical resources, but importantly also from very poor countries with very different cultural beliefs and traditions (Ammini et at. 2002; Warne and Raza 2008). It is clear that while outcomes in the technically advanced and better resourced countries are still far from perfect, they are dramatically better than in developing countries where services and medicines are in restricted supply, poverty and lack of education are widespread, and rumour and discrimination, based on ignorance, make people's lives a misery.

Many patients in developing countries are not given any treatment or counselling at all. There is a strong preference for male children in some countries and females born with genital abnormalities have a much lower chance of survival than males. 'Parents prefer the intersex children to be reared as male possibly because of the less social stigma attached to an impotent male than to sterile female, and because males are socially independent' (Rajendran and Hariharan 1995).

Within living memory, similar conditions prevailed in western societies and the degree to which progress has been made in the development of an holistic and collaborative approach to the management of DSD, built on great scientific advances, should be acknowledged. Patient advocacy groups should be proud of the positive influence they have had on the debate. Their relationships with the medical profession have improved greatly since they were established in the late 1990s and a healthy dialogue has developed.

Many long-term outcome studies (Rajendran and Hariharan 1995; Migeon et al. 2002a, b; Mazur et al. 2004; Reiner 2005; Warne et al. 2005a; Johannsen et al. 2006; Julka et al. 2006; Nihoul-Fékété et al. 2006; Brinkmann et al. 2007; Jürgensen et al. 2007) have looked at mixed groups of DSD subjects, based on the premise that everyone desires a good quality of life and therefore it is reasonable to study all of the patients treated in one institution as a single group, regardless of the different diagnoses, using very broad outcome measures (which have been reviewed by Zucker (2005)). Only a few (e.g., Warne et al. 2005a) have included a control group.

The management of DSD requires a multi-disciplinary team approach, properly funded, and working from a strong evidence base. Ideally, patient advocacy groups should be involved, and where relationships between local practitioners and local support groups have become frayed, mediation to achieve compromise and positive engagement would be helpful. More research into basic mechanisms of sex differentiation, the determinants of gender identity, and epidemiology is needed. Highly specialized diagnostic facilities should be centralized within countries and even regions, with provisions made to subsidize testing for the poorest of the poor. International collaborations to generate sufficient numbers for the study of very rare disorders are being established and should provide better information on which to base new management protocols.

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Complete Androgen Insensitivity Syndrome: A Guide for Parents and Patients

27

Garry L. Warne

27.1 Introduction

Some medical conditions are easy to talk about and some are more challenging. A condition like Androgen Insensitivity Syndrome (AIS), which affects the development of the genital and reproductive system, raises some very uncomfortable issues about gender identity that are difficult to put into words. How is it that a woman can be born without a womb and with testes? For generations, women with AIS, and their parents, have struggled to understand this apparent contradiction. Many would have had no idea that there were others with the same condition, unless the condition was ‘in the family’. Even then, discussion about a subject relating to genital development and sexual feelings may have been taboo.

We are now in an age when sexual matters are openly discussed in the media. This freedom is presenting opportunities for the community at large to be given some information about the existence and nature of AIS. The community will become more understanding and accepting of unusual medical conditions when they are better informed about them and the problems they cause. The same applies to women with AIS. It is a difficult condition to accept, but women will be helped if they have access to both good information about it and adequate opportunities to discuss the complex feelings that are bound to arise as this information is being absorbed.

This chapter has been prepared to provide women with AIS, and their families, with accurate medical information about this condition and guidance on how to find help.

27.2 How AIS Was First Recognised

The first medical report on AIS was published in 1953 by J. M. Morris, an American gynaecologist. His patient was a woman who had never menstruated. She had well-developed breasts and the external genitals of a normal woman, but she had only very sparse pubic hair and a swelling in each groin. An operation was performed, and in each of the swellings was a testis. The woman had no uterus and no ovaries. It is now known that women with AIS have the XY chromosome pattern usually associated with the male gender, and the Y chromosome causes testes to develop. In addition, they have a relatively short vagina. Because there is no uterus, there is also no cervix, and so the vagina ends as a pouch with no internal connections.

27.3 The Nature of AIS

AIS is just one of a number of medical conditions that affect the development of the reproductive and genital organs. It is caused by an alteration in a gene (a physical particle containing genetic information that is found in every cell in the body). This alteration in the gene blocks the body’s response to masculinising hormones (androgen) during foetal development and after birth. In other words, it makes the body insensitive to androgen, and masculine development that would

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occur in the presence of a normal gene is impossible. The whole syndrome (the combination of physical changes that are characteristic of AIS) results from this alteration in a single gene. The body can respond to feminising hormone (oestrogen) but not androgen.

There are two forms of AIS: *Complete* AIS (CAIS) and *partial* AIS (PAIS). CAIS is a condition in which the external genitals are completely female in appearance, but the internal female reproductive organs are missing. PAIS is a variant of AIS in which affected children are born with masculinised genitalia. The extent of this is variable: some babies have a slightly enlarged clitoris and a smaller than usual cleft between the labia, while others may have an almost fully formed penis and scrotum. Some children with PAIS are raised as girls, others as boys. The presence of testes and the absence of a uterus is characteristic of both CAIS and PAIS.

The problems associated with CAIS are in many ways different from those of PAIS. In CAIS, the sex at birth is clearly female, whereas the sex of a newborn infant with PAIS may be unclear and a decision must be made about whether to raise the child as a girl or a boy. Therefore, to avoid confusion, this chapter will only consider CAIS, and PAIS will not be discussed, although there is a lot of information about it elsewhere in this book, particularly Chap. 7.

There are many other disorders in which the development of the external and internal genital and reproductive organs is incomplete or in which both male and female organs are found together. One in every 4,500 newborn babies has external genitals that differ significantly from the standard male and female appearance. Most people would assume that such conditions are terribly rare because they do not read about them in the newspapers, but they are not.

In common parlance, much is made of the difference between the sexes. How different are they really? According to Eastern philosophy, the female and male attributes *Yin* and *Yang* are considered to coexist in perfect balance and harmony. Most people have some qualities that may be regarded as feminine and some that are masculine. In bodily structure and function, there are more similarities than differences between females and males. For example, all women produce masculinising hormone (androgen) and all men produce feminising hormone (oestrogen). In the development of the human foetus, there is a stage when the internal and external genitalia of females and males appear identical. This means that all differences between the sexes develop from a common starting point, a completely neutral stage. From there, development may proceed either along female or male lines. The genetic and hormonal control of female and male sexual development in the foetus is well understood, and much more is known about it than about how most other aspects of development are controlled. This detailed knowledge provides a solid framework on which to build a clear understanding of AIS.

27.4 Hormones

Hormones are the chemical messengers in the body. They are produced in one place by a hormone-producing gland, and act somewhere else in the body. Insulin, for example, is made in the pancreas and acts in the liver and the muscles to regulate the level of glucose in the bloodstream. Growth hormone is made in the pituitary gland near the brain and acts to promote bone growth in children.

27.4.1 Androgen

Androgen is a masculinising hormone that in males is responsible for the growth of the penis, development of facial and body hair, growth of the muscles and skeleton and deepening of the voice. Both males and females have androgen. In males, and in females with AIS, it comes from two sources: The testes and the adrenal glands (a pair of organs that lie above the kidneys, on the back wall of the abdomen). Nearly all of the androgen in females with the XX chromosome pattern comes from the adrenal glands with only a small contribution from the ovaries.

27.4.2 Androgen and Masculine Sexual Development

When babies begin their development in the womb, it is impossible to distinguish male genitalia from female. Figure 27.1 shows what these ‘neutral’ genitalia of both male and female look like. Note that in both sexes there is a midline cleft, with a button-like swelling at the top representing the future penis or clitoris.

Figure 27.1 shows what happens in boys at 12–15 weeks after conception, as their testes start producing androgen. The button grows into a penis,

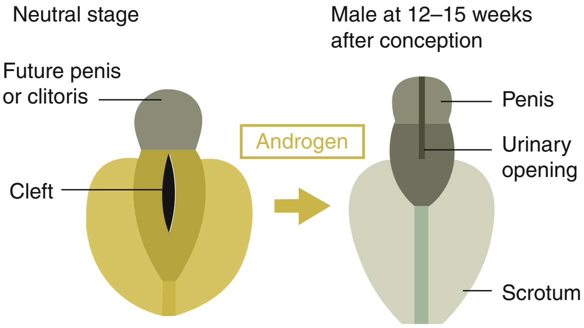

Fig. 27.1 Androgen causes the 'neutral' genitalia to become male

the cleft closes over, starting from the bottom. This causes the urinary opening to move progressively towards the tip of the penis, and the scrotum to form.

Figure 27.2 shows normal female genitalia. Because androgen is normally not produced in the female foetus, the clitoris remains small and the cleft remains open.

In CAIS, the testes produce androgen but the skin covering the genital structures, and the other genital tissues, are unable to respond in the normal way, which is to develop into a boy. It is as though the androgen was not produced at all. The external genitalia develop as in normal females because the natural direction of development in the foetus is to become female. Masculine changes only occur in response to androgen.

27.4.3 The Internal Reproductive Organs

At the beginning of foetal development, males and females have identical internal reproductive organs. In both sexes, there is a pair of tubes on the back wall of the abdomen that are capable of developing into the female uterus, fallopian tubes and the upper part of the vagina. These organs do not develop in males because the foetal testes produce a hormone (MIS or AMH) that blocks this process (Fig. 27.3).

The same things happen in females with CAIS: Their testes produce MIS/AMH which prevents development of the uterus, fallopian tubes and the upper part of the vagina.

The length of the vagina is variable between women with CAIS, for reasons that are still unclear. Even sisters who appear to have the same external features of CAIS may have quite different degrees of vaginal development.

27.4.4 Androgen Receptor Abnormality

In a foetus with CAIS, androgen does not have the usual masculinising effect on genital development. The reason is that its body cells lack a special anchoring substance called androgen receptor, and without androgen receptor, the cells cannot respond to androgen, no matter how much is present. It is a bit like a radio receiver that cannot be tuned to the frequency that is being transmitted. Not all hormone receptors are abnormal in CAIS, only androgen receptor. The oestrogen receptor is completely normal and therefore women with CAIS develop breasts and a feminine body shape.

Some females with CAIS have no androgen receptor at all, while in others it is abnormal and does not function as a receptor. A foetus with a small amount of *active* receptor (less than normal) will begin to develop as a boy but the process will not be completed; therefore, the baby will have the features of PAIS.

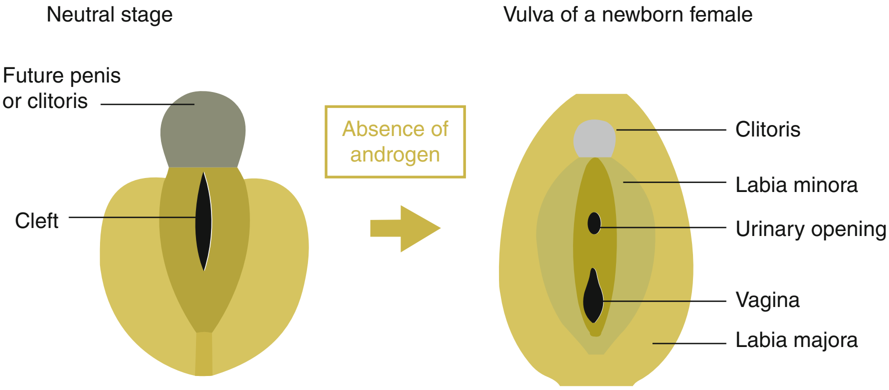

Fig. 27.2 In the absence of androgen, the genitalia change from 'neutral' into female

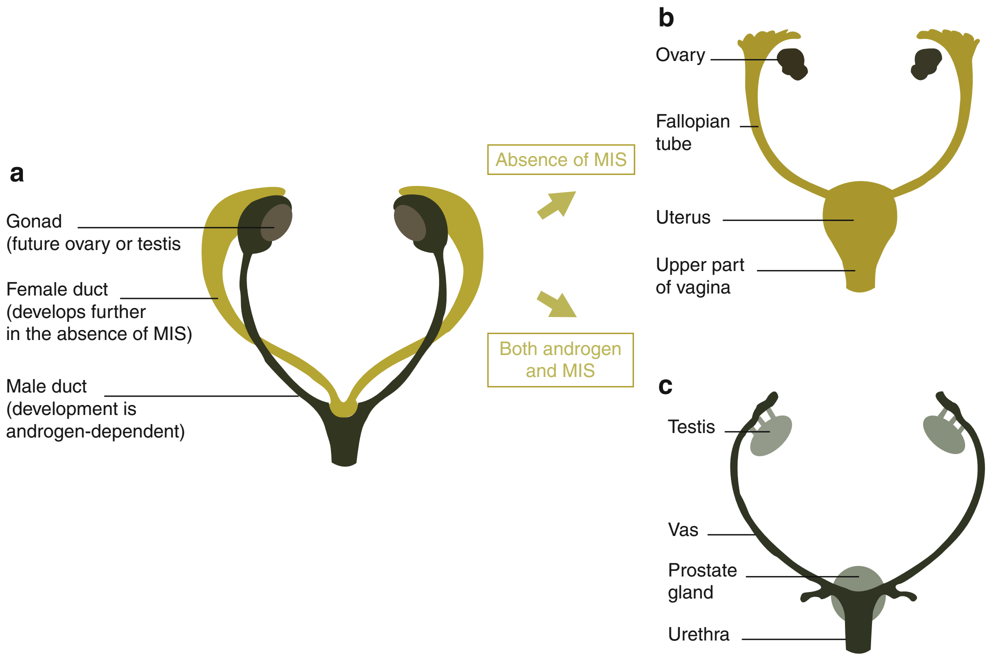

Fig. 27.3 Development of the internal reproductive organs in the female and male (**a**) Neutral stage in both males and females (**b**) Female organs develop in the absence of MIS/AMH (**c**) Male organs develop when both androgen and MIS/AMH are produced by the testes

27.5 The Genetic Basis of AIS

27.5.1 Chromosomes and Genes

Every new human being results from the fertilisation of an egg by a sperm. The characteristics of the father are contained in each individual sperm, and those of the mother in each of her eggs.

The sperm and egg cells contain about 100,000 tiny particles called genes. Each gene represents some characteristic of the parent that the child inherits.

When an egg has been fertilised by a sperm, the father's genes are added to the mother's, and the fertilized egg (the new human being) thus has two sets of genes. There is, for example, a gene from the mother and a gene from the father for the colour of the eyes. In fact, there is a pair of genes for every separate characteristic. The genes from the mother and father are nearly always paired, and these pairs are reproduced in every cell of the new person.

Genes are linked together on structures called chromosomes. Every cell in the body contains exactly 46 chromosomes. Two of these are sex chromosomes, which may be either X or Y. Females normally have two X chromosomes, while males normally have one X and one Y chromosome. The Y chromosome contains the gene that causes testes to develop (Fig. 27.4).

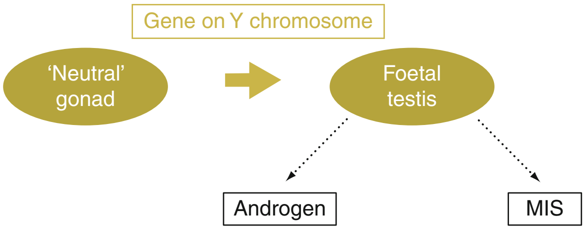

Fig. 27.4 Triggered by a gene on the Y chromosome, the 'neutral' gonad becomes a testis. It later produces two hormones, androgen and MIS/AMH

27.5.2 The Androgen Receptor Gene

Females with CAIS have an X and a Y chromosome. The Y chromosome is completely normal, therefore testes develop. The X chromosome is also normal, except that one of its thousands of genes has altered. This alteration is in the androgen receptor gene. A female will have two androgen receptor genes, one inherited from her mother and one from her father. If one of these is the altered, androgen receptor gene that causes CAIS, the normal gene on the other X chromosome will be sufficient to cause her to develop as a normal female. If, however, this woman has a child who is XY and who inherits the X chromosome bearing the altered gene, the abnormal gene will not be balanced by a normal gene and the child will be a female with CAIS. It should also be noted that in one-third of girls with CAIS, it is caused by a spontaneous genetic change in the newly-formed foetus at the time of conception, rather than being inherited.

27.5.3 The Inheritance of AIS

The following diagram shows the different chromosome combinations that can result when a mother who carries the CAIS gene on one of her X chromosomes has children (Fig. 27.5).

A couple who have a daughter with CAIS can use the genetic diagram above to predict the odds of having other affected children. The way the parents' genes were distributed at the time of a particular conception is completely independent of what will happen during the conception of a future child, just as each throw of dice is independent of every other throw. Therefore, the risk of having another child with CAIS is 1 in 4 for every pregnancy, assuming the mother to be a carrier.

27.6 The Diagnosis of CAIS

The physical features that initially suggest the possibility of CAIS differ from person to person, and these differences influence the age at which diagnosis of the condition is usually diagnosed. The most common feature is a bulge (a hernia) in the groin area in an otherwise normal baby or little girl. When it is operated on, the hernia is found to contain a testis. If hernias go unnoticed or are not present, it may not be known that there is anything wrong until she is a teenager, when she has not begun to menstruate and neither pubic nor underarm hair has appeared, although her breast development will be normal.

To confirm the diagnosis, a blood test is done to identify the XY chromosome pattern. The ability of

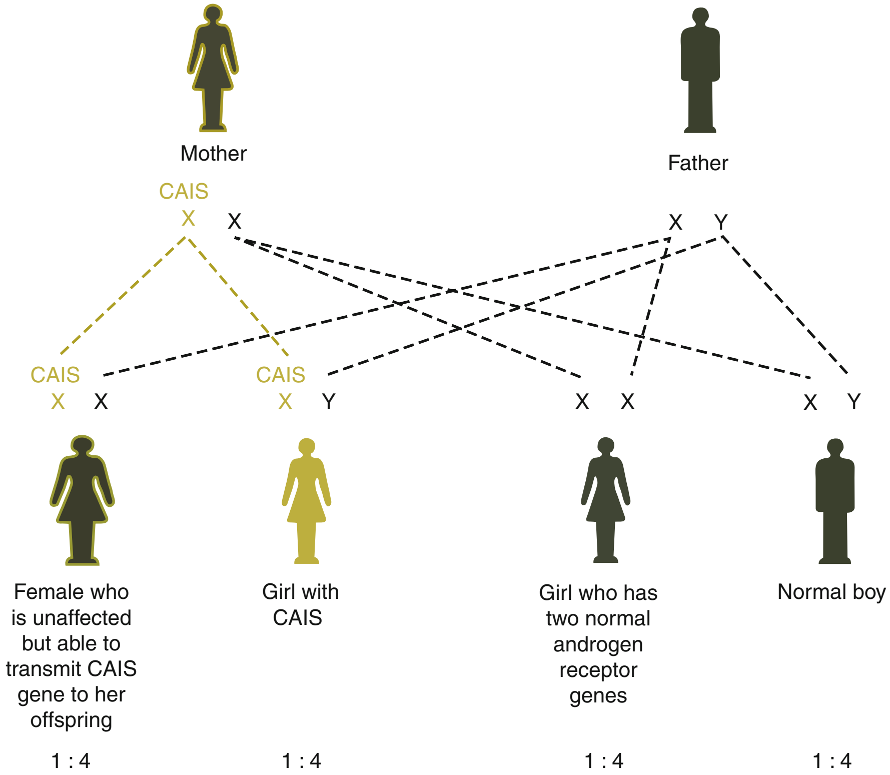
Mother
CAIS
X X
Father
X Y
CAIS
X X
CAIS
X Y
X X
X Y
Female who is unaffected but able to transmit CAIS gene to her offspring
Girl with CAIS
Girl who has two normal androgen receptor genes
Normal boy
1 : 4
1 : 4
1 : 4
1 : 4

Fig. 27.5 Genetic diagram showing how a mother who carries the CAIS gene on one of her X chromosomes can pass it on to her children. The risk of having a child with CAIS is 1 in 4 for every pregnancy

the testes to produce androgen can be measured in blood samples collected before, and 72 h after an injection of a hormone called human chorionic gonadotrophin (hCG), which stimulates the testes. This proves that testes, rather than ovaries, are present. The hCG test is also useful for distinguishing CAIS from other medical conditions in which an XY female has testes, but they cannot produce androgen. An ultrasound examination will establish that there is no uterus.

27.7 Hormonal Changes During Childhood and Adolescence

During childhood, the testes are dormant. When the girl is about 11–12, they are stimulated to develop by hormones made in the pituitary gland, a part of the brain. The testes gradually enlarge and the level of androgen they produce progressively rises to adult male levels. At the same time, however, the body converts some of the androgen to oestrogen, and this causes breast development and widening of the hips, so the body shape becomes that of a woman.

The conversion of androgen to oestrogen is a normal process in the body, and is not confined to girls with CAIS. Many healthy adolescent boys experience transient breast enlargement for the same reason. Boys, however, are fully responsive to androgen and this seems to inhibit further breast development.

Unlike many teenagers, girls with CAIS have very good skin with no acne (pimples). Acne occurs when oil-producing glands in the skin are stimulated by androgen, but this is impossible when the girl has AIS.

27.8 Surgery for Girls with AIS

27.8.1 Removal of the Testes

Testes that remain in the abdominal cavity, particularly those that are being over-stimulated by the pituitary gland, are prone to develop cancer. This develops in approximately 2% of women with AIS, but hardly ever before puberty. However, it is the opinion of most authorities that this risk of cancer after puberty is too high, and that removal of testes that are inside the abdomen before the age of 20 is advisable. Removal after puberty is a good option in terms of the girl's self esteem, because, due to the conversion of androgen to oestrogen in the body, she will develop breasts and a female body shape without the need for hormonal treatment. The surgery would take place after the girl had been fully informed about her medical condition, and after she had been given the opportunity to discuss the feelings that arise under these circumstances.

In the past, removal of the testes in early childhood was widely recommended, but this is now regarded as unnecessary as the risk of cancer is much lower than was previously thought and the benefits of retaining the testes until after pubertal development has occurred outweigh the risks. In addition, the girl can participate in the decision as full disclosure about the nature of AIS will empower her to contribute to the discussion. If, as is common, the testes are in the groin and can be examined directly, some experts are thinking that they can be retained because they produce valuable hormones and can be monitored for any change suggesting cancer by regular medical examination, assisted by ultrasound.

Early removal of the testes is essential in babies with partial AIS who are being raised as girls because failure to do so would result in progressive masculine development. In these girls, surgery to reduce the size of the clitoris and to separate the fused labia is also offered.

27.8.2 The Vagina

Usually the vagina of a woman with AIS is about 6 cm, which is two-thirds the normal length, but it can be much shorter than this. Girls with AIS therefore need to have their vagina examined to assess its length. While surgery may sometimes be necessary to lengthen it, the vagina also grows with regular sexual intercourse. Before a girl becomes sexually active, she can use dilators to gradually bring about some extension.

27.9 Lack of Pubic and Underarm Hair

The hair that XX women have in the genital and underarm areas is there because of the action of androgen produced in the adrenal glands and ovaries. Women with CAIS usually have either no hair at all in these areas, or very sparse hair. This lack of pubic hair is a physical characteristic that cannot be altered by medical treatment, but women may be able to develop positive ways of thinking about it. The amount of pubic hair that women generally have is very variable, and some women are relatively hairless. It has been reported that the mothers of women with CAIS have somewhat less pubic hair than women who do not carry the CAIS gene, so it can honestly be said that a lack of pubic hair is 'in the family'. In addition, some women choose to shave off their pubic hair. Others have a medical condition called 'alopecia totalis' that causes their body (and scalp) hair to fall out. In other words, there are a number of reasons other than CAIS for not having pubic hair – and for some people the absence of pubic hair is seen as erotic.

27.10 Oestrogen Replacement Therapy

Any girl over 12 years old with AIS who has had her testes removed needs to take a supplement of oestrogen, initially to induce development in her breasts, hips and genitalia, and to promote the deposition of calcium in her bones. Many girls with CAIS are tall because the Y chromosome carries genes for extra height, and oestrogen treatment, which accelerates the completion of growth in the growth plates (the zones of growing cartilage near the ends of children's bones), may be used to prevent excessive adult height. In addition, oestrogen replacement therapy is beneficial in reducing the risk of heart attack and stroke in post-menopausal women. For this reason, and because it prevents bone thinning (osteoporosis), women with AIS should take oestrogen all their lives.

Many different forms of oestrogen are available. Most commonly it is taken as a daily tablet, but skin patches that are changed every few days are also becoming popular. Small tablet-sized implants of hormone may be placed under the skin using local anaesthetic every 6 months, but these do not suit all women. Millions of women take oestrogen every day as it is a component of most oral contraceptives.

Oestrogens may have side effects for some women, such as weight gain, fluid retention, nausea and migraines. Women on high-dose oestrogen are also at increased risk of deep vein thrombosis (blood clots in the calf veins), but high doses are not required for women with AIS.

Commercially available contraceptive pills all contain a second hormone (a progestogen) which is there to induce regular changes in the lining of the uterus so that periods occur. Women who have no uterus do not need to take progestogen, and it is preferable for them not to do so because progestogens may have side effects such as depression, bloating and abdominal pain.

27.11 Counselling and Support

Better ways of understanding and working through the possible social and psychological effects of AIS are currently being developed, and many difficulties have been overcome. Nevertheless, parents are anxious to maintain confidentiality, and affected women may feel uncertain about how others will respond to them. The general public is unaware of the existence of AIS because there is little media coverage of it. Any lack of community understanding is likely to be due to ignorance rather than prejudice.

27.11.1 Parents of Newly Diagnosed Children

A medical diagnosis that affects the genital and reproductive organs is a particular challenge to understand, discuss and come to terms with in a helpful way. Since most families have never heard of anyone else with this kind of medical condition, they usually ask their doctors for help in finding words and ideas. At the same time, they must find ways of dealing with their own powerful emotions, which often include great pain, sadness and anger. 'Why me?' and 'Why my daughter?' are natural reactions.

Ideally, AIS should be correctly and promptly diagnosed, and an expert should be available immediately to provide counselling for the parents. This, however, is not always the case and parents may encounter hesitation and delays along the way. Not surprisingly, this generates confusion and anxiety. An opportunity to discuss these feelings with a professional who is familiar with the condition is often beneficial. Counselling takes the form of assistance to put words and ideas to the many powerful emotions that may be aroused. It is inevitable that parents will have stages of vulnerability as they adjust to a diagnosis with reproductive implications, and the child's future development will need to be discussed.

27.11.2 Parents of Older Children and Teenagers

When parents feel they can talk to their daughter about her medical condition and the feelings that arise, they can gradually help her to understand something of the nature of AIS. In the end, this should strengthen their relationship with her. Parents face a dilemma about how and when to tell their daughter about AIS. Should they provide all the information they have as early as possible, or delay telling her until in their judgement she is ready to hear the truth? The emerging view is that she has a right to know everything, but that information should be given in stages that take into account her level of development and ability to understand what is being said.

27.11.2.1 Children Aged 6–11 Years

Up to the age of 11, most children have little ability to think about long-term consequences, and a simple explanation about the reason for seeing the doctor will generally suffice. If parents have concerns about the questions or behaviours their child is presenting to them, they could have a discussion about her with a mental health professional interested and experienced in assisting parents and children with AIS-related issues.

27.11.2.2 Adolescents with AIS

Girls usually develop the ability to reason and to think in philosophical terms about the age of 12, although the timing of this varies from person to person. It is only at this stage that a girl with AIS will be able to understand a discussion about the complex nature of her condition, and even then, she will be quite unfamiliar with the internal workings of the body.

Adolescence is a stage associated with peer pressures to conform. It is preferable for girls with CAIS to learn about their differences compared to others before this pressure to conform becomes dominant. Children learn about genes and chromosomes in school at around the age of 15–16, and it is best for them to be informed about their own diagnosis before this time.

27.11.3 Adults

It is understandably difficult for many women with CAIS to accept the ways in which the disorder affects their lives and relationships. All medical conditions arouse complex feelings in people and their families, and relationships may at times come under strain as different family members adjust to the issues in their own way. Because it is a genetic condition, a woman with CAIS may have affected sisters, nieces or aunts who can provide mutual understanding and support.

Many women with AIS marry and adopt children. They and their partners know from the beginning that there will be no pregnancies and can plan their lives and careers accordingly. This may be less painful than the experience of the 10% of all married couples who find after years of marriage that one or other partner is infertile. Women with CAIS are found in all walks of life.

When required, counselling services are available and a referral from the doctor to a mental health professional or social worker will be arranged on request. Many women find it very helpful to meet other women with AIS.

27.11.4 Support Groups

Support groups for people with AIS and their families have recently been formed, and much invaluable information has come from affected adults, who are assisting the medical profession to find better ways of helping younger girls and women deal with their diagnosis. Regular newsletters are published, enabling the free exchange of views and experiences. This chapter is based on a booklet prepared with the assistance of the AIS Support Group (UK).

Additional Material

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